

Health Technology Assessment (HTA) of the Smaller-Incision New- Generation Implantable Miniature Telescope (SING IMT) for the management of patients with late-stage advanced age-related macular degeneration

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Contributions

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Abbreviations

AAO	American Academy of Ophthalmology
ACD	Anterior chamber depth
ADL	Activity daily living
ALE	Advanced lipid peroxidation products
AMD	Age-related macular degeneration
ARMS2	Age-related maculopathy susceptibility 2
APOE	Apolipoprotein E
BrM	Bruch's membrane
C2	Component 2
C3	Component 3
CDNVA	Corrected distance near visual acuity
CDVA	Corrected distance visual acuity
CFB	Complement factor B
CFH	Complement factor H
CFI	Complement factor I
CFP	Color fundus photography
CI	Confidence Interval
CNV	Choroidal neovascularization
CNVM	Choroidal neovascular membranes
CSC	Current standard of care
CUA	Cost-Utility Analysis
CUR	Health problem and current use of the technology
DSA	Deterministic Sensitivity Analysis
EA	Adverse event
ECD	Endothelial cell density
EC-IMTd	Endothelium-to-implant distance
EC-IPd	Endothelium-to-iris plane distance
ECO	Cost and cost-effectiveness
EFF	Clinical effectiveness
ETH	Ethical analysis
ETS	External Telescopic System
FA	Fluoroangiography
FAF	Fundus autofluorescence
FCP	Fundus-controlled perimetry

FDA	Food and Drug Administration
GA	Geographic atrophy
GWAS	Genome-wide association studies
HDL-C	High-density lipoproteins
IAMDGC	International AMD Genomics Consortium
ICGA	Indocyanine green angiography
ICUR	Incremental Cost-Utility Ratio
IMT	Implantable Miniaturized Telescope
iPSC	Induced Pluripotent Stem Cells
LEG	Legal analysis
LMI	Lipshitz Macular Implant
LY	Life Years
MAC	Membrane Attack Complex
NIA	Near-Infrared Autofluorescence
NIR	Near-Infrared Reflectance
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
ORG	Organizational Aspects
OVD	Ophthalmic Viscosurgical Device
PCR	C-Reactive Protein
PCV	Choroidal Polypoidal Vascular Disease
PDGF	Platelet-Derived Growth Factor
PDT	Photodynamic Therapy
PFA	Perfluoroalkoxy alkanes
PRL	Preferred Retinal Locus
PRN	Pro Renata Approach
PSA	Probabilistic Sensitivity Analysis
PS-OCT	Polarization-Sensitive Optical Coherence Tomography
PTFE	Polytetrafluoroethylene
RAP	Retinal Angiomatous Proliferation
ROS	Reactive Oxygen Species
RPE	Retinal Pigment Epithelium
rtPA	Recombinant Tissue Plasminogen Activator
SAF	Safety
SD-OCT	Spectral-Domain Optical Coherence Tomography

SING IMT	Smaller-Incision New-Generation Implantable Miniature Telescope
SIRE	Shallow Irregular RPE Elevation
SML	Scharioth Macular Lens
SOC	Social and Patient Aspects
SS-OCT	Swept-Source Optical Coherence Tomography
TAE	Treat-and-Extend Schemes
TEC	Description and Technical Characteristics
VA	Visual Acuity
VEGF	Growth Factor vascular endothelial
WTP	Willingness-to-pay

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Preface

The growing incidence of age-related macular degeneration (AMD), particularly in its advanced forms, represents one of the most significant challenges for health systems in countries with the highest levels of demographic ageing. In this context, technological innovation applied to the ophthalmology field stands out as a crucial opportunity to improve the quality of life of patients experiencing a progressive and often irreversible loss of central vision. Among the emerging solutions, the SING IMT (Smaller-Incision New-Generation Implantable Miniature Telescope) device offers a concrete answer to restoring visual autonomy in patients with limited remaining therapeutic options.

This report has been developed with the aim of providing an in-depth and structured analysis of the SING IMT technology using the Health Technology Assessment (HTA) methodology. This multidimensional approach makes it possible to evaluate not only the clinical effectiveness and safety of the device, but also the organizational, economic, social, and ethical impacts associated with its adoption. The assessment was conducted according to the Core Model® developed by EUnetHTA, which is recognized at the European level as a methodological benchmark for the comparative evaluation of health technologies.

The preparation of this document was supported by a systematic process of gathering and analyzing the available scientific evidence, combined with direct engagement with clinical experts and institutional decision-makers convened within a multidisciplinary Advisory Board. This was further complemented by the development of an economic model specifically adapted to the Italian context, designed to estimate the sustainability profile of the technology over the medium to long term.

The overall objective is to contribute, through a solid and methodologically transparent evidence base, to an evidence-informed decision-making process capable of balancing the value of innovation with the needs for sustainability and equity in the allocation of healthcare resources. This work aims to serve as a reference point for all stakeholders, clinicians, administrators, policymakers, and sector representatives, interested in rigorously and responsibly evaluating the introduction of innovative solutions for the management of chronic-degenerative ophthalmologic diseases.

Executive Summary

Background

Age-related macular degeneration (AMD) is the leading cause of irreversible central vision loss among individuals over 65 years old and represents a growing epidemiological and socioeconomic challenge in aging health systems. The advanced stages of the disease, geographic atrophy and disciform scarring, result in profound bilateral visual impairment that severely compromises autonomy and quality of life. In these conditions, standard therapeutic options (anti-VEGF, photodynamic therapy, and low-vision aids) are often ineffective or insufficient to restore functional vision.

The Smaller-Incision New-Generation Implantable Miniature Telescope (SING IMT™) represents an innovative intraocular solution specifically designed for patients with end-stage AMD. The device provides up to 2.7× magnification of the central visual field by projecting images onto healthier parafoveal retinal areas, thereby reducing the impact of central scotomas. SING IMT is implanted monocularly through a reduced corneoscleral incision using a preloaded delivery system, which improves surgical ergonomics and reduces risks compared with the earlier IMT model.

From a classification and healthcare data traceability perspective, the procedure can be identified through specific coding systems (e.g., ICD-9-CM code 13.91 – *Impianto di lenti telescopiche intraoculari, impanto di telescopio miniaturizzato*), although the availability and integration of coding and reimbursement schemes may vary across healthcare settings, with potential implications for access and data comparability.

This Health Technology Assessment (HTA) was conducted according to the multidimensional EUnetHTA Core Model®, integrating clinical evidence, safety data, economic evaluation, organizational considerations, and ethical and social perspectives. The objective is to support decision-makers by offering a comprehensive, methodologically robust evaluation of the potential adoption of SING IMT within the Italian healthcare system.

Clinical Effectiveness

In a severe, highly disabling condition with major unmet needs, SING IMT consistently demonstrates, across recent clinical studies, meaningful improvements in both distance and near visual acuity. Average gains range from +10 to +15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters within 3–6 months, with over half of patients achieving ≥3 lines of improvement. Near vision, often unmeasurable at baseline, improves significantly due to effective magnification of functional retinal loci. Structured visual rehabilitation is essential to maximize functional adaptation, with evidence showing marked gains in reading acuity, reading speed, and fixation stability. Early data from

pseudophakic patients also confirm visual improvements, expanding potential applicability.

Safety

The safety profile is acceptable, although not free of risk. The most frequent postoperative events are transient corneal edema, inflammatory deposits, iris-related complications, and fluctuations in intraocular pressure. Persistent endothelial cell loss ranges from 8–12% in the first six months. Most complications resolve with medical therapy, yet a minority of patients experience persistent symptoms, such as blurred vision or double vision, that may lead to device explantation. Careful patient selection and strict postoperative follow-up remain key to minimizing adverse outcomes.

Quality of Life and Patient-Reported Outcomes

SING IMT leads to substantial improvements in disease-specific quality of life, including better performance in daily activities such as reading, facial recognition, watching television, and overall autonomy. Studies using the Low Vision Quality of Life questionnaire (LVQoL) show significant increases in visual-function scores within three months. However, patient satisfaction depends on both objective gains and subjective tolerance of the altered visual experience. A small proportion of patients may report dissatisfaction even in the absence of clinical complications.

Economic Evaluation

From a healthcare system and societal perspective, SING IMT shifts resource use toward an upfront investment (surgery plus rehabilitation), potentially reducing downstream costs associated with low-vision disability and assistive technologies. The cost-utility analysis compares SING IMT with current standard of care (CSC) over a lifetime horizon. Preliminary estimates, based on international evidence adapted to the Italian context, suggest that the technology may be cost-effective under standard willingness-to-pay thresholds (€40,000/QALY), especially in younger elderly patients (65–74 years) who are more likely to maintain long-term visual gains.

Organizational Impact

Implementing SING IMT requires specialized surgical expertise, access to dedicated equipment, and the establishment of structured postoperative rehabilitation pathways. Multidisciplinary collaboration among ophthalmic surgeons, low-vision specialists, and rehabilitation therapists is essential for optimal outcomes. While the procedure increases

initial surgical workload, it may reduce long-term reliance on fragmented low-vision services and caregiver support.

Ethical Analysis

Based on the available evidence, the benefit–risk profile of the SING IMT appears favorable in carefully selected patients and in settings capable of ensuring experienced surgery, structured rehabilitation, and multidisciplinary follow-up. Compliance with the principles of beneficence and non-maleficence is contingent upon stringent operational conditions, including rigorous patient selection, comprehensive information, realistic expectation management, and careful monitoring of complications, within a framework of prudence and continued evidence generation.

The positive impact may also extend to the family and social sphere, albeit in the presence of potential indirect burdens. Respect for patient autonomy requires a thorough informed consent process, active patient involvement, and an ongoing relationship with the care team. Overall, the SING IMT supports an efficient reallocation of resources toward an investment with high clinical and social value, provided that the technology is introduced within a framework of institutional responsibility and attention to equity.

Social Analysis

The social analysis focused on the following items: patients' expectations. To date, no specific studies are available in the literature regarding patients' expectations and preferences concerning the use of the technology in question. However, it is reasonable to assume that patients' expectations are understandably high, as they are linked to the anticipated recovery of vision and, consequently, to overall autonomy and the ability to resume daily and social activities; caregiver burden.

AMD, particularly in its advanced stages, leads to disability and loss of independence, requiring caregiver support. Such support is also necessary in the immediate postoperative period following SING IMT implantation and during rehabilitation. Since the technology in question may significantly improve the quality of life of patients with AMD, this benefit may extend to caregivers in terms of a progressive reduction in care burden, as well as in the emotional and psychological stress associated with managing severe patient disability; communication with patients to ensure treatment adherence. Communication by clinical staff in the pre- and postoperative phases should be timely, realistic, and clear, facilitating the responsible exercise of patient autonomy and the consequent expression of informed, free, and voluntary consent/adherence to the use of the technology in question. This communication concerns three categories of stakeholders: (1) the patient; (2) caregivers; (3) the broader community; patient access to the technology. The principle of justice, grounded in the values of the Italian National Health Service (SSN), in principle justifies universal availability of effective and safe treatments for AMD.

In summary, access to SING IMT may be limited by: concentration of the technology in a small number of highly specialized centers, resulting in geographical inequalities; “selective” clinical eligibility criteria; socioeconomic barriers and caregiver burden; and cultural, cognitive, informational, and communication barriers.

Legal Analysis

The legal analysis defines the regulatory compliance framework within which the SING IMT™ may be implemented, in full respect of the fundamental rights of the person. Pursuant to Italian Law No. 219/2017, implantation requires free and informed consent based on complete, comprehensible, and personalized information regarding benefits, risks, alternatives, and the rehabilitation commitment. The surgical and transformative nature of the procedure makes a structured communication process essential.

Given the advanced age of the target population, assessment of decision-making capacity is of central importance; in cases of legal incapacity, partial incapacity, or the presence of a legal guardian/support administrator, consent is provided in accordance with Article 3 of Law 219/2017, while giving due consideration to the person’s residual capacities. Access to the technology must be ensured in compliance with the principles of equality and protection of health, avoiding indirect discrimination.

The device, CE-marked and classified as a Class IIb implantable medical device, is subject to Regulation (EU) 2017/745 and to vigilance and post-market surveillance obligations. Therefore, the legal compatibility of the SING IMT is contingent upon implementation that complies with requirements concerning informed consent, safety, and professional responsibility.

Objective

The objective of this report is to systematically and multidimensionally analyze the SING IMT technology, intended for patients with advanced-stage AMD for whom conventional therapeutic options prove to be ineffective or no longer applicable. Through the use of the HTA methodology, the analysis aims to assess the device's clinical effectiveness and safety profile, integrating these findings with economic, organizational, social, and ethical considerations. The goal is to provide a rigorous knowledge base, contextualized to the Italian healthcare system, to support strategic decisions regarding the potential adoption and diffusion of the technology, while ensuring the appropriate use of resources and a targeted response to currently unmet clinical needs. The analysis is conducted with full scientific independence, through the collection of clinical evidence, the development of economic models, and the involvement of experts and stakeholders in a validation process of the results.

Literature review

As part of the project, a review of the currently available scientific literature was conducted, and the results were further enriched with grey literature sources and scientific evidence identified through a manual search.

Methods

The research question was formulated using the PICO model, which includes the study population (P), the intervention under evaluation (I), the comparator (C), and the outcome of interest (O).

Errore. L'origine riferimento non è stata trovata. describes the PICO model underlying this research. The research question aimed to investigate the safety and effectiveness aspects, as well as the organizational and economic impact profile, of the SING IMT device (**Errore. L'origine riferimento non è stata trovata.**).

Table 1 – PICO model

Population (P)	Patients with advanced AMD with severe visual impairment and a limited response to conventional treatments
Intervention (I)	Smaller-Incision New-Generation Implantable Miniature Telescope
Comparators (C)	NA
	Safety
	Efficacy
Outcomes (O)	Economic impact
	Organizational impact
	Ethical and social impact

To gather the evidence needed for a comprehensive assessment of the technology under investigation, in March 2025 a search string, defined on the basis of the outlined PICO model (Errore. L'origine riferimento non è stata trovata.), was launched across the main scientific databases (**Errore. L'origine riferimento non è stata trovata.**).

Table 2 – Research string

<pre> ((((((((("Macular Degeneration"[Mesh]) OR ("Macular Degeneration*") OR ("Macular Dystroph*") OR ("Maculopath*") OR ("Age Related Macular Degeneration*") OR ("Age-Related Macular Degeneration*") OR ("Age Related Maculopath*") OR ("Age-Related Maculopath*") OR (AMD))) AND (((("Small-incision new- generation implantable miniature telescope") OR ("SING IMT") OR ("Implantable miniature telescope") OR ("IMT") OR ("WA IMT")) </pre>
--

The database used was PubMed. No search filters were applied regarding time limits, language, or study type

Inclusion & exclusion criteria

The scientific evidence identified through the search strategy was considered eligible unless it met one or more of the following exclusion criteria:

- duplicate studies;
- studies addressing a technology not under investigation;
- studies concerning health conditions not under investigation;
- studies involving a population not under investigation;
- study types not relevant for the analysis (editorials, preclinical studies);
- insufficient information reported in the study on any of the aspects investigated;
- abstract/full text not available;
- study not available in English or Italian.

The identified studies were classified using an Excel® spreadsheet containing, for each study:

- an identification code indicating the database from which the evidence originated;
- whether it was a duplicate;
- the first author;
- the year of publication;
- the title;
- the DOI reference;
- the link to the abstract.

The domains considered for the development of the Full-HTA Report are listed below:

- Health problem and current use of the technology (CUR);
- Description and technical characteristics (TEC);
- Safety (SAF);
- Clinical effectiveness (EFF);
- Cost and economic effectiveness (ECO);
- Organizational aspects (ORG);
- Ethical analysis (ETH);
- Social and patient aspects (SOC).

The results of the literature review were discussed and assigned to the most appropriate

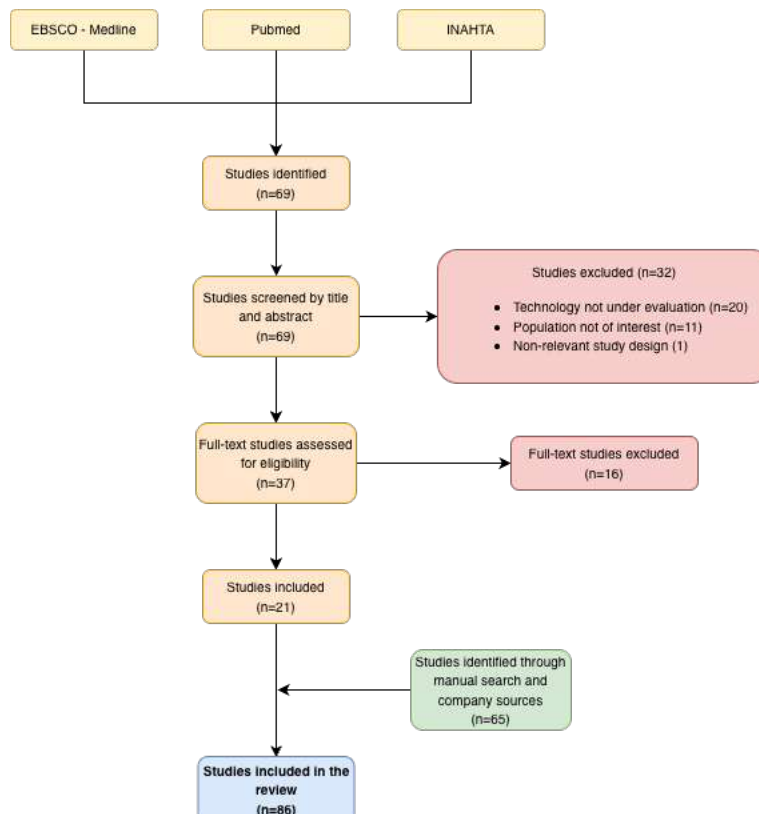
domains based on their relevance to the topics and questions defined by the EUnetHTA Core Model[®] 3.0.

Results of the literature review

The search strategy identified a total of 69 records on 28 March 2025. Based on the exclusion criteria defined above, 32 records were excluded during the first screening for the following reasons: technology not under investigation (20); population not under investigation (11); non-relevant study type (1). During the second screening, using the same exclusion criteria, an additional 16 studies were excluded.

In conclusion, a total of 21 studies were included in the review, distributed across the domains CUR (1), TEC (0), SAF/EFF (19), ECO (1), ORG (0), ETH/SOC (0); some studies were included in more than one domain. In addition, a manual search was conducted, and some documents were provided by the company.

Figure 1 – PRISMA model. Illustrative diagram of the literature review process



CUR Domain

Health problem & current use of technology

Topic & Issue

Health problem & current use of technology (CUR)

Table 3 – Topic & Issues Health problem & current use of technology (CUR)

Topic	Issue	Assessment element ID
Target Population	What is the target population for this assessment?	A0007
	How many people are in the target population?	A0023
Target Condition Current Disease Management	What is the disease or health condition being assessed?	A0002
	What are the known risk factors for the disease or health condition?	A0003
	What is the natural course of the disease or health condition?	A0004
	What are the symptoms and burden of the disease or health condition for the patient?	A0005
Use Target Population	What are other typical or common alternatives to current technology?	A0018
	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	A0024
	How is the disease or health condition currently managed according to published guidelines and in practice?	A0025
Target Condition	For which health conditions and populations and for what purposes is the technology used?	A0001

Target population

A0007 – What is the target population for this evaluation?

The target population for this assessment consists of individuals affected by AMD, particularly those in the intermediate and advanced stages of the disease. This population is primarily composed of individuals over 65 years of age, a group in which the prevalence of AMD increases significantly with age, exceeding 44% among those aged 70 to 95. Neovascular AMD is the most common advanced form and occurs more frequently than geographic atrophy (GA) (1).

Although AMD represents a very large population in Italy, the group eligible for implantation is much more restricted. The inclusion criteria considered in the studies and in the device's indications for use define a specific population: patients ≥ 55 years old with advanced and irreversible AMD (geographic atrophy or disciform scar involving the fovea), corrected distance visual acuity between 20/80 and 20/800, visually significant cataract, anterior chamber depth ≥ 2.5 mm, and axial length > 21 mm.

Additionally, patients must have good peripheral vision in the fellow eye and must demonstrate, through a preoperative evaluation using an external telescope, a minimum benefit of 5 ETDRS letters.

These clinical and functional requirements substantially narrow the target population compared to the broader universe of AMD patients, with important implications for comparison with other therapeutic or rehabilitative options (1–2).

From the perspective of procedure classification and traceability within healthcare information systems, the implantation of the miniature intraocular telescope can be identified in the ICD-9-CM classification by code 13.91 (Implantation of a miniature telescope, including removal of the crystalline lens by any method), within category 13.9 "Other operations on the lens." The use of this code may support the identification of treated patients in administrative databases and facilitate comparative analyses across different settings. However, the availability and application of specific coding and reimbursement systems may vary across countries and healthcare systems. In particular, the recent introduction of this technology implies that, in some settings, it may not yet be fully integrated into existing tariff systems, with potential implications for access, uptake, and cross-country data comparability.

A0023 – How many people belong to the target population?

Globally, AMD represents one of the leading causes of visual disability. In 2015, it was the third most common cause of moderate to severe visual impairment, with a prevalence of 8.7% among individuals aged 45 to 85 years and 0.4% for the advanced form (2). The dry form of AMD accounts for approximately 80–85% of cases and is associated with a relatively more favorable visual prognosis, whereas the wet (neovascular) form, although representing only 15–20% of cases, is responsible for about 80% of severe vision loss related

to the disease (3). The global prevalence of AMD is expected to increase from 196 million people in 2020 to 288 million by 2040 (2).

AMD is more common in the European population than in the Asian population and is less frequent among individuals of African origin. In industrialized countries, it is the leading cause of irreversible vision loss in people over 65 years of age and accounts for about 9% of all cases of blindness. For example, in Germany, between 2002 and 2017, early AMD cases increased from 5.7 to 7 million (+23%), while advanced cases rose from 360,000 to around 490,000 (+36%). The neovascular form is 1.4 times more frequent than GA (the end stage of the dry form) (4).

In Italy, AMD affects approximately 1 million people, 200,000–300,000 of whom present with advanced forms. Around 63,000 new cases are reported every year, with an increasing impact driven by progressive population ageing. Furthermore, diagnosis is often late, especially for the initial dry form, which may remain asymptomatic for a long time (5–6).

Target condition

A0002 – What is the disease or health condition under assessment?

The disease under assessment is AMD, a chronic, progressive degenerative condition that affects the macula, the central portion of the retina responsible for detailed central vision required for daily activities such as reading, driving, and facial recognition.

From an anatomico-pathological perspective, the disease involves the photoreceptor/retinal pigment epithelium (RPE)/Bruch's membrane (BrM)/choroid complex. The most marked alterations occur in the macula but are not confined exclusively to this area (3, 7). AMD initially manifests with subretinal deposits known as drusen, aggregates of extracellular material that accumulate between the RPE and Bruch's membrane, impairing the transport of nutrients and metabolic waste. Drusen contain a complex mixture of plasma proteins, lipoproteins (apolipoprotein E), cholesterol-rich lipids, amyloid P, glycoproteins, and complement system components, particularly the membrane attack complex (MAC), which promotes a chronic local inflammatory state contributing to RPE and photoreceptor degeneration.

Drusen can be classified as:

- *hard* (<65 µm, with sharp borders);
- *soft* (>65 µm, with indistinct borders and irregular shape, associated with disease progression);
- *mixed* (presence of both types);
- *based on diameter* (small <63 µm, medium 63–124 µm, large >125 µm).

Another key element in the pathogenesis is the accumulation of lipofuscin, an autofluorescent pigment produced by the incomplete metabolism of photoreceptor outer segments by RPE phagolysosomes. Lipofuscin, and particularly its toxic fluorophore A2-E,

contributes to photoreceptor apoptosis, activation of the complement cascade, and RPE atrophy, with secondary drusen formation.

The pathogenesis of AMD therefore includes multifactorial mechanisms: alterations in lipid metabolism, subclinical chronic inflammation, oxidative stress, microvascular damage, mitochondrial dysfunction, and a significant genetic component. Genetic variants in complement system genes (factor H, CFH; factor 3, C3; factor 2, C2; factor B, CFB; factor I, CFI), as well as in ARMS2 (age-related maculopathy susceptibility 2), HTRA1 and APOE (apolipoprotein E), are strongly associated with AMD. In particular, the CFH Y402H and ARMS2 A69S variants are responsible, alone or in combination, for over 80% of advanced AMD cases, with up to a 50-fold increased risk in individuals homozygous for both alleles.

From a clinical perspective, AMD initially presents in an early form with drusen and pigmentary changes; at advanced stages, it can evolve into:

- a *dry or atrophic form*, the more common one, characterized by non-exudative, irreversible GA, which cannot be treated with currently available therapies;
- a *wet or neovascular form*, less frequent but more aggressive, caused by the growth of choroidal neovascular membranes (CNVM) induced by vascular endothelial growth factor (VEGF), responsible for exudation, hemorrhage, and rapid vision loss (3, 8).

A0003 – What are the known risk factors for the disease or health condition?

The known risk factors for AMD are numerous and include non-modifiable, environmental, metabolic, and genetic elements, as well as complex cellular mechanisms related to retinal ageing, particularly involving RPE cells.

Among non-modifiable factors, age is the most important: the risk of developing AMD increases exponentially with ageing, especially after 55 years of age. Ageing of RPE cells leads to a disruption of the enzymatic balance in the extracellular matrix of the macular region, with accumulation of metabolites on BrM, resulting in damage to adjacent retinal tissues, reduction of blood flow, and formation of vitreous excrescences (“vitreous warts”). These processes promote cellular senescence, production of pro-angiogenic factors such as VEGF, and structural alterations such as calcifications and breaks in BrM, which facilitate the neovascularization typical of advanced AMD.

Oxidative stress is another key factor in AMD pathogenesis, as the retina, with its high oxygen consumption, is particularly susceptible to damage from reactive oxygen species (ROS). The accumulation of lipofuscin in the RPE, with its toxic fluorophore A2-E, contributes to increased oxidative stress, cell death, and activation of the complement cascade. Prolonged exposure to sunlight appears to increase the risk of AMD, likely due to the phototoxic action mediated by ROS.

Lipid metabolism also plays an important role: elevated levels of high-density lipoprotein cholesterol (HDL-C) are associated with greater AMD risk, whereas total cholesterol and

LDL-C appear to have a protective role. Advanced lipid peroxidation products (ALE), present in lipofuscin and vitreous excrescences, interfere with protein stability and induce apoptosis of photoreceptors and RPE cells.

Local inflammation and complement system dysfunction are major early markers and pathogenic mechanisms in AMD. C-reactive protein (CRP) levels are elevated in patients and interact with complement factor H, whose 402H variant impairs complement regulation, favoring uncontrolled activation, inflammation, and angiogenesis. The C5a component, released during complement activation, crosses Bruch's membrane, causing inflammation and stimulating neovascularization. Choroidal neovascularization (CNV) is promoted by increased levels of pro-angiogenic factors such as VEGF and Platelet-Derived Growth Factor (PDGF), along with reduced inhibitory cytokines. Thickening of BrM increases choroidal vascular resistance, reducing blood flow and promoting the formation of new pathological vessels. Choroidal vitreous excrescences and abnormal pigmentation further increase AMD risk.

Finally, other mechanisms such as reduced autophagy in senescent RPE cells contribute to the accumulation of lipofuscin and protein aggregates, accelerating cellular degeneration. The hemodynamic theory posits that vascular dysfunction of the choroid, with thickening and sclerosis of vessel walls, leads to insufficient perfusion of the RPE and retina. Alterations in circadian rhythm and imbalances in proteostasis are also being investigated as potential factors related to AMD (9).

Among environmental risk factors, cigarette smoking is the most significant, increasing the risk of AMD two- to four-fold through mechanisms that include oxidative stress, inflammation, altered lipid metabolism, and reduced plasma antioxidants. Smoking cessation gradually reduces this risk over time.

Other environmental and behavioral risk factors include diet and physical activity. A diet rich in lutein, zeaxanthin, and omega-3 fatty acids is associated with a reduced risk of advanced AMD, whereas regular physical activity, even at low or moderate intensity, is correlated with a slower disease progression.

Regarding metabolic and cardiovascular factors such as hypertension, diabetes, obesity, and hyperlipidemia, the evidence remains inconsistent and not yet clearly defined.

Finally, genetic susceptibility plays a fundamental role in the development and progression of AMD, with family aggregation and twin studies estimating heritability of up to 71% for the late form of the disease, a value higher than that of many other complex age-related conditions.

Genome-wide association studies (GWAS) have identified more than 50 independent genetic variants associated with late AMD, located in at least 34 genomic loci. Among these, the two main risk loci are:

- CFH, on chromosome 1, particularly the rs1061170 (Y402H) variant, which has been shown to significantly increase AMD risk. The 402H allele is associated with reduced complement regulatory capacity and thus with uncontrolled activation of the complement cascade, resulting in local inflammation and retinal damage;

- ARMS2 and HTRA1, two genes located on chromosome 10 in strong linkage disequilibrium with each other, making it difficult to distinguish which variant is causally responsible. Both are strongly associated with late AMD and neovascular phenotypes.

Heterozygous and homozygous variants in these genes confer multiple risks: for example, heterozygous CFH Y402H increases AMD risk by about 4.6 times, while the homozygous variant increases it up to 7.4 times compared with non-carriers. For ARMS2 A69S, the heterozygous variant leads to a 2.7-fold increased risk, while the homozygous variant is associated with an up to 8.2-fold increase. In addition, a significant additive effect has been observed when both risk alleles are present, resulting in up to a 50-fold increased risk of AMD.

Beyond CFH and ARMS2, other complement-related genes are associated with AMD, including CFB, C2, C3, CFI, and genes involved in lipid metabolism such as APOE.

Some rare high-penetrance variants in loci such as CFH, CFI, and TIMP3 have provided stronger evidence of causality. The use of cellular models, such as induced pluripotent stem cells (iPSC), has made it possible to study in isolation the specific effects of certain genetic variants on the RPE, although these models still fail to fully reproduce the complexity of the human disease.

More recent studies, such as those conducted by the International AMD Genomics Consortium (IAMDGC), have estimated that the identified variants account for about 27% of the overall risk of late AMD, while the remaining heritability remains partly “missing”, likely due to yet unidentified genetic factors, gene–environment interactions, or epigenetic mechanisms.

From a phenotypic perspective, genetic variants are associated with different subtypes and stages of the disease. For example:

- ARMS2-HTRA1 variants are associated with a higher risk of GA and with faster enlargement of GA areas;
- the risk variant in C3 is associated with slower GA enlargement;
- CFH and ARMS2-HTRA1 variants are also correlated with distinct phenotypes such as extramacular drusen, peripheral reticular pigmentary changes, subretinal and sub-RPE hemorrhages.

Genetic stratification also reveals that the impact of risk variants may be modulated by age and sex, with some variants exerting stronger effects in younger patients.

The genetics of AMD display unusual features: a few loci confer a high risk and account for a large portion of heritability, while many other loci with modest effects contribute more marginally. This peculiarity, together with phenotypic complexity and interaction with environmental and metabolic factors, underlines the need for integrated and personalized approaches to risk assessment and clinical management of the disease (7).

A0004 – What is the natural course of the disease or health condition?

Clinically, AMD presents in two main forms: the dry (or degenerative) form and the wet (or neovascular) form. The dry form accounts for about 80% of cases and generally involves both eyes, causing mild to moderate visual loss. Its progression is usually slow, but in some cases it may evolve into a more aggressive neovascular form.

GA is the advanced manifestation of the dry form, accounting for about 35% of all advanced AMD cases and contributing to 20% of legal blindness related to the disease. By contrast, the neovascular form, also known as disciform, is characterized by abnormal growth of new blood vessels beneath the retina, which can lead to more severe damage and rapid vision loss.

From an evolutionary standpoint, disease progression can be divided into three main stages according to the AREDS classification:

1. *Early*, with small signs such as areas of hyperpigmentation and a few medium-sized drusen;
2. *Intermediate*, with the presence of larger drusen and possible GA outside the macula;
3. *Advanced*, including both the dry form with extensive atrophy and the neovascular form with subretinal neovascularization.

In clinical practice, AMD severity is often assessed based on visual acuity (VA), classified as mild, moderate, severe, or very severe according to Snellen test results.

The population with early or intermediate AMD is large and growing, with estimates indicating more than 8 million affected individuals at these stages alone. Of these, about 1.3 million are expected to develop the advanced form over the next five years, with consequent significant visual loss and reduced quality of life (8).

A0005 – What are the symptoms and disease severity for the patient?

The initial symptoms of AMD are often subtle and mainly involve difficulty performing visual tasks in low-light conditions or low-contrast environments. Patients frequently report problems such as difficulty seeing in the dark or in variable lighting, with reduced contrast sensitivity, which can interfere with daily life (7, 10). The more evident signs that prompt patients to seek medical attention include visual distortion (metamorphopsia), with straight lines appearing bent or wavy, blurred vision, and loss of central vision, often associated with a defect in the visual field. During the early and intermediate stages of AMD, symptoms may be mild or even absent, with drusen being the predominant finding

in the macula. At these stages, patients may experience mild distortion, difficulty focusing while reading, or reduced contrast sensitivity (3).

In dry, or non-exudative, AMD, patients often begin to experience difficulties with night vision or adapting to rapid changes in lighting conditions, with day-to-day fluctuations in vision. Metamorphopsia tends to develop slowly, and RPE changes are observed, with accumulation of basal laminar deposits that may evolve into GA with progressive loss of photoreceptors and reduced visual capacity. Areas of atrophy increase over time, causing stable central scotomas that compromise reading, facial recognition, and other fine visual tasks, while sparing peripheral vision.

In contrast, in exudative, or wet, AMD, symptoms are more rapid and pronounced, with acute or subacute worsening of central vision, quickly developing metamorphopsia, and central scotomas often caused by subretinal hemorrhages and fluid accumulation. Formation of CNVM leads to disruption of the barrier between the choroid and the retina, resulting in RPE detachment, hemorrhages, subretinal fluid, and thickening of retinal tissue. These changes are responsible for a progressive and often rapid loss of central vision, severely limiting daily activities. Localized atrophy in the macula causes scotomas that may slowly enlarge and then stabilize. Wet AMD typically presents asymmetrically but involves both eyes, with individual variability in symptom severity and progression. In addition, an association has been reported between AMD and neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, independently of the patient's lifestyle (11).

Current management of the disease

A0018 – What are the other typical or common alternatives to the technology under assessment?

AMD is a chronic, progressive disease and represents the main cause of low vision in developed countries. It presents in two distinct clinical forms: the atrophic (dry) form, which slowly but inexorably progresses to GA, and the neovascular (wet) form, characterized by abnormal growth of choroidal neovessels that rapidly compromise visual function.

In recent years, major therapeutic advances have been achieved in the treatment of wet AMD, thanks to the introduction and development of anti-angiogenic drugs that have revolutionized the visual prognosis of patients. These drugs act mainly by inhibiting VEGF, considered the primary mediator of ocular angiogenesis. The first anti-VEGF approved by the Food and Drug Administration (FDA) was pegaptanib sodium in 2004, but its use rapidly declined due to its selectivity for only one VEGF isoform. Subsequently, ranibizumab (2006), a monoclonal antibody fragment capable of inhibiting all VEGF-A isoforms, showed significant VA improvements in pivotal studies such as MARINA and ANCHOR.

In parallel, bevacizumab, a full-length antibody initially approved for oncological use, was adopted off-label in ophthalmology due to its efficacy comparable to ranibizumab and markedly lower costs, as demonstrated in the CATT trials. Aflibercept, a fusion protein

approved in 2011 in the United States and in 2012 in Europe, binds VEGF-A, VEGF-B, and PlGF, enabling less intensive treatment regimens (one injection every two months after the loading phase). The VIEW 1 and VIEW 2 trials demonstrated its non-inferiority compared with ranibizumab.

Among the more recent drugs, brolucizumab, thanks to its low molecular weight, provides better tissue penetration and prolonged dosing intervals, although it has been associated with an increased risk of vasculitis and retinal vascular occlusion. Faricimab, on the other hand, is the first dual-acting drug that inhibits both VEGF-A and angiopoietin-2, ensuring more durable vascular suppression and allowing, in selected patients, extension of injection intervals up to 16 weeks.

The mode of administration of these drugs is a crucial aspect in the management of neovascular AMD. Fixed monthly dosing schemes represent the standard for achieving the best visual outcomes but entail a high burden for patients and health systems. Treat-and-extend (TAE) regimens, which involve injection at every visit with progressively extended intervals, represent an effective compromise. The pro re nata (PRN) approach, in which treatment is administered only upon recurrence of neovascular activity, reduces the number of injections but requires frequent monitoring and may lead to inferior long-term outcomes. Flexible, cyclic regimens have also been developed, such as treatment every three months alternated with breaks, or the “observe-and-plan” strategy based on individual clinical course (2–3, 9, 11).

Alongside anti-VEGF drugs, some complementary therapies remain in use. Photodynamic therapy (PDT) with verteporfin, activated by low-intensity laser light, is used in selected cases of choroidal neovascularization, such as polypoidal choroidal vasculopathy, sometimes in combination with anti-VEGF agents. Studies have shown that combining ranibizumab and PDT can improve VA and reduce macular thickness compared with monotherapy. Surgical techniques such as neovascular membrane removal or macular translocation are now rarely used due to their invasiveness and disappointing visual outcomes. However, in selected cases of massive subretinal hemorrhage, pneumatic displacement of blood by intravitreal gas injection may be employed, sometimes combined with recombinant tissue plasminogen activator (rtPA) to promote clot lysis (3, 9).

Treatment of AMD, both in the dry and wet form, has also evolved significantly thanks to the introduction of various special intraocular lenses designed to improve central vision in affected patients. These implants represent an innovative solution, particularly for those who no longer benefit from pharmacological therapies or external lenses. Among the most advanced devices currently in use are the IOL-VIP systems, the Lipshitz macular implant (LMI), the Fresnel prism lens, the iolAMD system, and the Scharioth macular lens. Each technology is based on different optical principles, aimed at optimizing central visual quality without compromising peripheral or binocular vision.

The IOL-VIP system is based on an intraocular Galilean-type telescopic concept and involves the implantation of two lenses: a highly negative biconcave IOL (approximately –66 diopters) placed in the capsular bag, acting as the ocular lens, and a highly positive biconvex IOL (approximately +55 diopters) positioned in the anterior chamber, acting as the

objective lens. Both lenses are made of polymethyl methacrylate and feature ultraviolet light-filtering properties. The optics of both IOLs measure 5 mm in diameter with a maximum thickness of 1.5 mm. The system provides an estimated distance magnification of about 1.3×. Before implantation, a capsulorhexis of at least 6 mm and a corneal incision enlarged to 7 mm are required to facilitate insertion. Candidate selection is performed using dedicated software and includes an intensive two-week preoperative training, followed by a three-month rehabilitation program aimed at consolidating the preferred retinal locus (PRL). Clinical results reported on 40 eyes of 35 patients showed a significant improvement in VA, with a mean postoperative VA of 0.77 logMAR compared with 1.28 preoperatively. No serious complications occurred, except in one case of pupillary block successfully treated with Nd:YAG iridotomy, which was subsequently adopted as a preventive procedure for all patients. Although the presence of two IOLs may raise concerns about increased risk to anterior ocular structures, at 20 months the corneal endothelium showed a mean cell loss of only 7%, indicating good tolerability.

Another interesting approach is represented by the Lipshitz macular implant (LMI), initially developed in a configuration similar to a Cassegrain telescope. This implant combines two reflective micro-mirrors integrated into the intraocular lens, capable of providing central magnification of up to 2.5× while preserving peripheral vision. Early studies on six eyes of six patients, four of whom had AMD, demonstrated an average VA improvement of about 3.66 lines and a significant increase in near reading ability. A more advanced version, called LMI-SI, was subsequently developed to be implanted over a standard IOL already present in the capsular bag. This new lens has an optic diameter of 5 or 6 mm and haptics similar to those of a traditional IOL, but with greater thickness. Implantation requires an incision of about 5 mm followed by a surgical peripheral iridectomy. Although data on postoperative visual efficacy are limited, the optical principle remains the same: to improve central vision without compromising peripheral perception.

The Fresnel prism intraocular lens works differently and is designed to optically shift the retinal image away from the central scotoma to a functioning retinal area, without physically moving the retina itself. This non-foldable PMMA implant, with a power of +20 D, has a Fresnel prism integrated into the posterior surface that shifts the image by about 6°, corresponding to approximately 1.8 mm on the retina. Used in three patients with advanced dry AMD, the lens subjectively reduced perception of the central scotoma, although improvements in VA were not dramatic. None of the patients reported diplopia, but one reported preferring vision in the non-operated eye. It is important to emphasize that correct positioning of the prism depends on accurate preoperative identification of the preferred retinal locus, which requires careful planning.

The iolAMD device represents a major step forward in the field of injectable telescopic IOLs. Also based on a Galilean system, it uses two hydrophobic acrylic lenses: a highly negative lens (-49 D) implanted in the capsular bag and a highly positive lens (+63 D) implanted in the ciliary sulcus, with an intentional decentration of 0.85 mm to shift the retinal image by about 3° from the fovea. The system is designed to be inserted with a standard cartridge through a 3 mm incision. In a study of two patients (three eyes), VA improved significantly

at both near and distance, with no relevant complications and no signs of implant instability during three months of follow-up. In another larger study involving 18 eyes, the device demonstrated a mean gain of 67% in decimal VA at four months. In some cases, lens replacement was required due to anterior dislocation. The main limitation is the lack of a range of available optical powers, making the device suitable only for patients with an axial length between 21 and 23 mm.

Finally, the Scharioth macular lens is a solution focused exclusively on improving near vision in pseudophakic patients. This monobloc hydrophilic acrylic IOL features a central 1.5 mm zone with a +10 D add, designed to be implanted in the ciliary sulcus even many years after cataract surgery. Implantation requires only a 2.2 mm incision and does not interfere with peripheral or binocular vision at standard reading distances. Binocular function may be temporarily compromised only at very close distances (about 15 cm), but without causing diplopia. The best results are obtained in patients with a minimum corrected distance visual acuity (CDVA) of at least 0.1 (12).

Despite these various proposals, it should be noted that these intraocular lens systems haven't yet entered routine clinical practice, and their use remains limited. Although several approaches have been developed over the past years and some early results are encouraging, these devices have not achieved widespread implementation in standard AMD management.

A0024 – How is the disease or health condition diagnosed in accordance with the Guidelines?

According to the American Academy of Ophthalmology (AAO) guidelines, the main goals in managing AMD are to prevent or slow visual loss and to improve the patient's overall visual function. Diagnostic assessment of a subject with signs or symptoms suggestive of AMD requires a comprehensive evaluation that includes all elements of the adult eye examination, with particular attention to those aspects specifically associated with this condition (13).

Medical history plays a central role and must include systematic collection of vision-related symptoms reported by the patient, such as metamorphopsia (distorted image perception), reduced VA, central scotomas, photopsias, and difficulty adapting to darkness. It is also essential to gather information on current pharmacological treatments and supplements, ocular and general medical history, any allergies, and particularly family and social history, with special attention to cigarette smoking, a known risk factor for AMD progression (10).

The physical examination includes the use of the Amsler grid for subjective detection of metamorphopsia, stereoscopic biomicroscopic examination of the macula, and, where necessary, binocular slit-lamp biomicroscopy with bright light, which is useful to identify subtle signs of neovascularization such as hemorrhages, exudates, subretinal fluid, edema, subfoveal fibrosis, and RPE changes. Color fundus photography (CFP), often performed in combination with angiography, is a useful complementary tool to document the presence

of drusen, GA, serous detachments, and other alterations, as well as to provide a baseline for long-term monitoring of the disease, especially in non-neovascular forms.

Among instrumental techniques, optical coherence tomography (OCT) is the cornerstone for diagnosis and follow-up of AMD. By using low-coherence light, OCT acquires high-resolution cross-sectional images of the retina, allowing visualization of intraretinal or subretinal fluid, RPE detachment, macular thickening, hyperreflective bands (such as shallow irregular RPE elevation – SIRE), and other morphological indicators of active disease. In atrophic forms (dry AMD), OCT allows documentation of the presence and evolution of drusen, including pseudodrusen (reticular drusen), thinning of outer retinal layers, and progression of GA. Advanced technologies such as spectral-domain OCT (SD-OCT), swept-source OCT (SS-OCT), and polarization-sensitive OCT (PS-OCT) further improve spatial resolution and the ability to visualize retinal and choroidal structures in depth.

These are complemented by OCT angiography (OCT-A), which enables non-invasive visualization of retinal and choroidal vasculature through motion contrast analysis. OCT-A is particularly useful in detecting CNVM, including at a subclinical stage, allowing identification of pathological vessels in the absence of visible fluid or obvious symptoms. Although it has not yet completely replaced traditional angiographic techniques, OCT-A offers sensitivity and specificity comparable to fluorescein angiography in diagnosing active CNVM and is particularly effective when combined with structural OCT. It also allows the study of choriocapillaris perfusion and CNVM evolution over time.

Fluorescein angiography (FA), an invasive diagnostic technique based on intravenous administration of sodium fluorescein, remains a reference method for CNVM characterization. It is indicated in the presence of suggestive symptoms or clinical signs of active disease and allows classification of CNVM type (classic, occult, mixed), extent, and location (subfoveal, juxtafoveal, extrafoveal), thereby guiding therapeutic choice and post-treatment monitoring. However, FA may cause adverse events, including allergic reactions, nausea, vomiting, and, rarely, anaphylaxis. Moreover, fluorescein crosses the placenta and appears in breast milk for up to 72 hours, requiring caution in pregnant or breastfeeding patients.

Indocyanine green angiography (ICGA) allows visualization of choroidal vasculature and is particularly useful in cases of occult CNVM, RPE detachments, retinal angiomatous proliferation (RAP), and in the diagnosis of polypoidal choroidal vasculopathy (PCV), more frequent in individuals of Asian and African origin. Compared with fluorescein, indocyanine green offers better tissue penetration due to its longer wavelength and is associated with a significantly lower risk of severe adverse reactions. It does not cross the placenta and is considered safe during pregnancy.

Fundus autofluorescence (FAF), obtained using blue light, allows assessment of RPE integrity and the distribution of lipofuscin, an autofluorescent pigment that reflects retinal metabolic damage. This examination has proven useful in detecting and monitoring GA and in predicting disease progression through the analysis of specific autofluorescence patterns. FAF may be complemented by near-infrared autofluorescence (NIA), which highlights melanin accumulation and is particularly sensitive in identifying pseudodrusen,

often not visible with other techniques. The integration of FAF, NIA, and near-infrared reflectance allows a more complete structural and functional analysis of the retina and its progressive degeneration.

Among functional tools, microperimetry allows point-by-point assessment of retinal sensitivity, correlating functional data with autofluorescence and OCT images, while fundus-controlled perimetry (FCP) has proven useful for measuring early rod damage, which is often affected before cones in AMD. Adaptive optics, although not yet widely used in routine clinical practice, enables ultra-high-resolution imaging of individual photoreceptors and retinal capillaries and appears promising for early diagnosis and for understanding pathogenic mechanisms.

Finally, there is growing interest in artificial intelligence for automated processing of retinal images and the development of predictive algorithms capable of identifying patients at high risk of progression. Although still undergoing clinical validation, these tools may in the future represent an important decision-support aid in personalized AMD management (10–11, 14)

A0025 – How is the disease or health condition managed according to guidelines

AMD is a chronic ocular disease and one of the leading causes of central vision loss in the elderly population. In particular, its neovascular form, if not managed promptly and effectively, leads to major clinical consequences and a substantial economic impact, not only for the patient but also for caregivers and the entire healthcare system. According to the most authoritative guidelines and a large body of scientific evidence, disease management requires an integrated and personalized approach centered on early diagnosis, appropriate therapeutic intervention, continuous monitoring, and careful attention to lifestyle.

An essential aspect in the fight against AMD is timely diagnosis, as detecting the disease at an early stage enables intervention before irreversible retinal damage occurs. For this reason, it is strongly recommended that at-risk patients, such as those with a family history of AMD or already affected by early forms, be educated to perform regular self-assessment of vision using simple tests such as the Amsler grid or home electronic devices. The importance of undergoing periodic, comprehensive eye examinations cannot be overstated, as these allow early identification of progression signs, even when symptoms are not yet evident.

When the neovascular form of the disease develops, treatment must be initiated as soon as possible. Available therapies are based mainly on intravitreal injections of anti-VEGF drugs, which have dramatically changed the prognosis of wet AMD. Key clinical trials such as ANCHOR, MARINA, VIEW, CATT, and HARBOR have demonstrated the efficacy of these drugs, validating different administration strategies. In particular, fixed-interval regimens have been shown to provide stable outcomes but pose a significant management burden,

whereas personalized protocols such as PRN or TAE aim to balance clinical efficacy and sustainability. The latter approach, now widely used in clinical practice, allows gradual extension of injection intervals while maintaining disease control. The most recent drugs, such as high-concentration aflibercept and faricimab, make it possible to maintain visual gains with less frequent injections, thereby contributing to improved quality of life for patients.

Management of AMD also requires special attention to potential complications, such as subretinal hemorrhages. Smaller hemorrhages can often be successfully treated with the same anti-VEGF therapies, whereas more extensive hemorrhages call for more complex evaluation. In these cases, therapeutic options include procedures such as pneumatic displacement of the hemorrhage, use of rtPA, or vitrectomy, but available evidence does not yet allow standardized protocols to be established, and approaches therefore remain case-specific (13).

Beyond pharmacological treatment, another pillar of disease management involves preventing progression in patients with dry AMD, particularly in early or intermediate stages. It has been shown that certain lifestyle changes can significantly influence disease evolution. Smoking cessation, for example, is one of the most effective measures to reduce progression risk, and direct advice from physicians has proved to be a key stimulus for long-term cessation. Regular physical activity, maintaining a healthy body weight, and adherence to a healthy diet based on Mediterranean principles are also associated with a lower risk of developing advanced AMD. In particular, a diet rich in fruits, vegetables, legumes, fish, and olive oil, and low in red meat and processed foods, appears to exert a protective effect. International studies, including the EYE-RISK project, have shown a positive correlation between adherence to the Mediterranean diet and reduced AMD incidence, confirming earlier observations from Europe and the United States.

In this context, the use of nutritional supplements plays an important role, particularly in patients with bilateral intermediate AMD or advanced disease in one eye. The AREDS1 and AREDS2 studies showed that specific combinations of antioxidants and vitamins can slow disease progression. However, it was found that β -carotene, included in the original AREDS1 formulation, increases the risk of lung cancer in smokers and former smokers; for this reason, the AREDS2 formulation, which excludes β -carotene, is preferred in these subjects. Other nutrients of interest include lutein and zeaxanthin, found in egg yolks and leafy green vegetables, which appear to exert a protective effect on the retina, as well as omega-3 fatty acids found in oily fish, although their preventive efficacy through supplementation has not yet been fully confirmed.

Protection from intense sunlight, particularly blue light, is another recommended measure, although the exact mechanisms by which high-energy light may damage the retina remain under investigation. Finally, factors such as sleep quality and body composition, including visceral obesity, have been associated with AMD risk, suggesting that a truly comprehensive approach to the disease should also take these elements into account.

When the disease progresses to forms that significantly impair visual function, guidelines recommend timely referral to low-vision rehabilitation services. This support can help patients maintain autonomy and a good quality of life despite visual limitations (15–16).

Utilization

A0001 – For what purpose, health condition, and population is the technology used?

AMD is a degenerative retinal disease and one of the leading causes of vision loss in the elderly population. In mild to moderate neovascular AMD, several therapeutic options are available, such as intravitreal injections of anti-VEGF drugs, laser treatment, and photodynamic therapy, which aim to slow disease progression and preserve residual visual function. However, in end-stage cases, defined by bilateral visual impairment ranging from moderate ($\leq 20/80$) to profound (20/600 or worse), due to central scotomas linked to GA or disciform scars, these interventions are no longer effective.

For dry AMD, treatment focuses on preserving photoreceptors and inhibiting the complement cascade, with the goal of delaying disease progression. In this context, vitamin supplementation is a commonly used approach, although it is also ineffective in more advanced stages, where vision loss is already severe. In these cases, patient management is essentially based on low-vision rehabilitation. Traditional rehabilitation technologies include optical and electronic aids such as magnifying lenses, prismatic glasses, handheld telescopes, closed-circuit television systems, and combined optical systems. Although useful, these tools have significant limitations: they provide a restricted visual field, require complex head or hand movements that may cause vestibular symptoms, and are often unsuitable for patients with motor or cognitive impairments. Despite these difficulties, many patients are motivated to try them in order to improve their residual visual ability (17).

To overcome the limitations of extraocular aids, implantable devices such as intraocular implants have been developed to provide stable intraocular image magnification and improve central vision by exploiting healthy peripheral retinal areas. One of the most promising solutions in this field is the implantable miniature telescope (IMT), designed specifically for patients with end-stage AMD, both in dry and wet forms. This device magnifies the image and projects it onto undamaged retinal areas, allowing improved near and distance vision. However, IMT implantation results in a significant reduction of the visual field in the treated eye, making the complementary use of the fellow eye essential for peripheral vision, and requires a specialized postoperative rehabilitation program to adapt to the new visual scheme (18).

In 2020, an improved version of the device, called SING IMT™, was approved in the European Union. It is designed to provide up to 2.7× magnification of the central visual field and a simplified implantation procedure thanks to a preloaded insertion system that requires smaller incisions. SING IMT is indicated for monocular implantation in patients aged at least 55 years, with stable VA between 20/160 and 20/800, affected by bilateral end-

stage AMD. This technology is therefore targeted at an elderly population with severe or profound visual loss no longer treatable with conventional therapies and addresses the clinical need to improve residual visual function and autonomy in daily activities through an innovative intraocular approach that is potentially more effective than external aids (19).

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TEC Domain

Description of the technical characteristics of the technology

Topic & Issue

Description of the technical characteristics of the technology (TEC)

Table 4 – Topic & Issues Clinical problem

Topic	Issue	Assessment element ID
Characteristics of the technology	What type of technology is it and what are the comparators?	B0001
	What is the stated benefit of the technology compared to comparators?	B0002
	Who can decide on and use the new technology?	B0004
Regulatory Status	For which indications has the new technology received authorization or the CE mark?	A0020
Other	Who produces the technology?	A0022

Characteristics of the technology

B0001 – What type of technology is it and what are the comparators?

The SING IMT™ system, NG SI IMT 3X model, represents an advanced technological evolution of the previous IMT, developed to improve the quality of implantation, reduce surgical complications, and optimize visual outcomes in patients with advanced-stage AMD. It is composed of two main elements: a miniaturized intraocular telescopic implant and a single-use, sterile, preloaded delivery system that allows precise, safe, and controlled placement of the device inside the eye.

The NG SI IMT 3X implant is a glass optical visual prosthesis which, also exploiting the natural refractive properties of the cornea, functions as a true intraocular telescopic system. The device integrates two quartz glass microlenses and a flexible medical-grade silicone haptic support, which ensures stability within the capsular bag after removal of the crystalline lens by phacoemulsification.

Once implanted, the telescope magnifies images from the central visual field, projecting them onto healthy retinal areas adjacent to the damaged macula, thereby reducing the impact of the central scotoma. This allows patients to recognize faces, read text, view images, and carry out daily activities with greater independence. The device is optimized for viewing at distances between 3 and 10 meters, while conventional spectacles can be used for near or distance vision. The effective visual field can reach up to 12° (equivalent to approximately 36° on the retina), with a nominal telescope field of about 20°, corresponding to 54° of retinal projection.

Among the main advantages of the NG SI IMT 3X is the ability to use normal eye movements for fixation and scanning of the environment, avoiding the fatiguing use of head movements. The internal placement of the device eliminates optical aberration and vestibular conflict issues typical of external devices, offering a more natural and stable vision.

The insertion system (IMT Delivery System) consists of a sterile, single-use cartridge and an injector, both supplied in a sealed blister and sterilized with ethylene oxide. The cartridge is preloaded with the implant, simplifying the steps of lubrication, loading, and insertion. The materials used, both in the implant and in the delivery system, are all medical grade and compliant with international biocompatibility standards (ISO 10993), and include quartz glass, silicone, polycarbonate, perfluoroalkoxy alkanes (PFA), polytetrafluoroethylene (PTFE), and stainless steel. The presence of stainless-steel components makes the implant conditionally compatible with magnetic resonance imaging (MRI).

From a surgical perspective, the SING IMT introduces significant improvements compared with its predecessor, but the operative procedure requires extreme care to ensure successful implantation. Preliminary short-term safety and effectiveness data are promising, as are recent in vitro assessments.

A critical aspect is the incision technique: it must not be performed on clear cornea in order to avoid surgically induced astigmatism (SIA), which with the older IMT could exceed 10 diopters. A continuous suture is preferable, as it helps limit SIA induction. However, an excessively posterior scleral incision can make intraoperative manipulation difficult, increasing the risk of iris prolapse and complications during phacoemulsification.

It is also essential to perform a continuous, centered 6 mm capsulorhexis: a capsulorhexis that is too small may lead to incorrect haptic positioning in the ciliary sulcus, causing telescope tilt; conversely, an overly large capsulorhexis increases the risk of implant dislocation. Complete aspiration of the cortex is also crucial, since any subsequent capsulotomies can only be performed via pars plana vitrectomy.

Another delicate step is the correct orientation of the cartridge during implant injection: the tip must be introduced at an angle of 50° relative to the iris plane. If positioned incorrectly, some haptics may exit the capsular bag; in such cases, a surgical hook can be used to apply gentle pressure at the base of the haptic to reposition it inside the bag. Because the cartridge tip is poorly visible, an overly deep insertion may cause posterior capsular rupture or luxation of the entire implant.

A particularly important aspect concerns protection of the corneal endothelium, which is one of the main intraoperative concerns. To prevent endothelial damage, two types of Ophthalmic Viscosurgical Device (OVD) are used: a dispersive one in the anterior chamber and a cohesive one in the capsular bag. Despite these precautions, studies on the previous IMT reported endothelial cell loss of up to 25% per year. The SING IMT has been redesigned to reduce its impact on the endothelium, but no clinical data have yet been published to support this. It is therefore essential to avoid any postoperative inflammation, as chronic iritis can worsen cell loss: anti-inflammatory therapy must be followed scrupulously.

Finally, careful patient selection is essential for procedural success. After implantation, the patient will lose stereoscopic vision and must undergo dedicated visual rehabilitation sessions aimed at teaching them how to correctly use the new system for fixation, reading, and spatial orientation (1–2).

Within the landscape of implantable solutions for AMD, alongside the SING IMT implantable miniature telescope, there is a heterogeneous group of intraocular devices that share the goal of improving central visual function in low-vision patients, while adopting different optical and surgical approaches. These systems include magnifying intraocular lenses (IOLs) such as Intraocular Lens for Visually Impaired People (IOL-VIP), Intraocular Lenses for Age-related Macular Degeneration (IOL-AMD), and EyeMax Mono, as well as “add-on” devices such as the Scharioth macular lens (SML). They represent possible alternatives in selected patients based on clinical, functional, or anatomical characteristics. In this context, each device is characterized by specific technical features, mechanisms of action, and indications for use, contributing to a diversification of the surgical approach to the management of advanced-stage AMD.

IOLs are designed to improve central vision through magnifying optical principles or by redistributing the retinal image. Within this category, three main systems stand out: IOL-

VIP, IOL-AMD and EyeMax Mono, each with different technical and optical characteristics but sharing the objective of improving visual function in low-vision patients (4–5).

The IOL-VIP system exploits a Galilean optical principle through the combined use of two intraocular lenses: a high negative power IOL positioned in the capsular bag and a high positive power IOL placed in the anterior chamber. Together with the cornea, these lenses form a magnifying optical system with an overall power of approximately +53 diopters, capable of providing about 1.3× magnification for distance vision. The system requires a relatively large incision, up to 7 mm, and precise axial alignment to avoid optical decentration. It has the advantage of preserving peripheral vision and thus represents an alternative solution for selected patients, especially in the presence of central scotomas (6).

The IOL-AMD system is similar in principle, also using a Galilean design with two implanted lenses, but it employs soft materials and a configuration that allows one lens to be implanted in the capsular bag and the other in the ciliary sulcus. The magnification achieved is comparable with that of the IOL-VIP system (approximately 1.25–1.3×), but with lower surgical complexity. Preliminary clinical studies have reported stable improvements in VA without serious complications. However, production of the device has been discontinued, currently limiting its availability.

Table 5 – Comparison of intraocular devices for AMD

	Indication	Incision size	Degree of magnification	Visual results	Safety profile	Rehabilitation requirement
IOL-VIP	Advanced AMD with macular degeneration	Up to 7 mm	~1.3x	Improved BCVA, distance, and reading; limitations if PRL changes	Risk of increased IOP, corneal edema, pain, PCO, astigmatism	Long pre- and post-operative adaptation times
IOL-AMD	Advanced AMD	3 mm	1.25–1.3x (~30% reduction in field of view)	Mean CDVA 0.12 → 0.20 at 4 months; fixation stable	Some cases of elevated IOP, vaulting; currently no longer produced	Limited, less complex than IOL-VIP
EyeMax Mono	AMD (associated cataracts, various stages)	2–3 mm	1.1–1.2x (image optimization)	Series of 244 cases: improvements in VA and quality of life	Safe, few complications (elevated IOP in some cases)	Does not require extensive rehabilitation
SML	Advanced atrophic AMD, pseudophakic patients	2.2 mm	+10D central (~3× at 15 cm)	CNVA improved ≥3 lines at 15 cm; CDVA unchanged	Good safety profile, no major complications	Minimal rehabilitation, focused on close-up reading
SING IMT	End-stage AMD (geographic atrophy or bilateral disciform scarring)	6.5–7.5 mm	2.7x	≥3 lines BCVA in ~60% of cases; ADLs improved; stable	Less endothelial cell loss (7.9%); less astigmatism and sutures	Intensive rehabilitation required (3–6 months)

A more recent and technologically different proposal is EyeMax Mono, a single-piece, soft, hydrophobic acrylic intraocular lens designed to optimize image quality over a broad macular retinal area, rather than only at the central fovea. This design allows the exploitation of peripheral macular regions even in the presence of foveal damage, supporting the development of new preferred retinal loci (PRL).

Finally, the SML represents a significant innovation in the field of intraocular solutions for the treatment of advanced AMD, offering a therapeutic option specifically aimed at improving near vision in selected patients. Designed specifically for pseudophakic subjects, the SML is configured as an “add-on” lens, intended to be implanted in the ciliary sulcus in addition to a pre-existing intraocular lens placed in the capsular bag. Implantation can be performed either at the time of cataract surgery or at a later stage, through a small corneal incision of approximately 2.2 mm, making the surgical procedure minimally invasive.

From a structural standpoint, the SML is a foldable, single-piece lens made of hydrophilic acrylic material, with an overall diameter of 13 mm. Its optical peculiarity lies in the central 1.5 mm zone, which provides an additional refractive power of +10 diopters, specifically calibrated to enhance near vision. Thanks to its mechanism of action, the Scharioth lens can offer a substantial benefit for reading and for tasks that require near vision, typically at a distance of 10 to 15 centimeters from the eye, without compromising distance vision. This feature makes it particularly suitable for patients who, despite reduced foveal function, retain sufficient residual capacity to benefit from the selective magnification effect provided by the lens (4–5).

Errore. L'origine riferimento non è stata trovata. summarizes the main characteristics of the different intraocular devices used in visual rehabilitation of patients with AMD considered in this analysis.

B0002 – What is the claimed benefit of the technology in relation to comparators?

The intraocular solutions previously described in the section on comparators present important limitations: in particular, although IOLs provide a certain degree of magnification, the usable visual field is extremely narrow, often less than 5°, and the fixation field is very limited. Eye movements are not very effective, and the patient must again rely on head movements to explore the visual environment. Furthermore, the optical complexity of the system and the need to combine the intraocular lens with an external spectacle lens introduce an additional level of difficulty in adaptation and use (7).

To these devices we may add the SML, indicated exclusively for pseudophakic eyes and not recommended in the presence of ocular conditions such as wet macular degeneration, iris neovascularization, progressive glaucoma, zonulopathies, or central corneal opacities. Its effectiveness depends on the residual presence of foveal or parafoveal function, since its optical mechanism magnifies an image centered precisely in the damaged foveal region rather than recruiting peripheral retinal areas. Despite the benefits offered, SML

implantation is contraindicated in the presence of concomitant pathologies such as uveitis, central corneal opacities, or zonular weakness. In rare cases, a risk of glare has also been reported. An additional aspect to consider concerns the overall impact on quality of life. Although it provides clear benefits in terms of near visual acuity, improvements in daily functioning have not yet been extensively documented. Only one study has assessed this parameter using the VFQ-25 questionnaire, reporting an average improvement of 28% in daily activities and a return to normal reading in approximately 35% of treated subjects (4–5).

In this scenario, characterized by devices often burdened by functional compromises and poor tolerability, the SING IMT telescope represents a substantial and innovative evolution of the original IMT implant. The new version was developed to enhance the optical and functional performance of the device, make the surgical procedure less invasive, and increase patient acceptability. Unlike previous optical aids, which are often bulky, unaesthetic, and poorly tolerated, the SING IMT is implanted entirely within the eye, improving both the visual experience and the patient's quality of life. Its optical configuration enables up to 2.7× magnification of the central visual field, making it particularly useful for activities such as reading, face recognition, or using digital devices.

One of the SING IMT's major strengths lies in its ability to maintain a wide and natural fixation field. While external telescopes require slow, wide head movements to explore the visual environment, the SING IMT allows normal eye movements to shift fixation, enabling smoother and less fatiguing vision, especially during prolonged visual tasks. This is made possible by the absence of mechanical constraints between the device and the outside of the eye, unlike systems combining contact lenses or intraocular lenses with external optics, which stabilize the retinal image and prevent the patient from correcting alignment through simple ocular saccades.

From a vestibular perspective, the SING IMT also offers significant benefits. In external devices, image magnification creates a distortion between perceived and actual motion, generating sensory conflicts between the visual and vestibular systems, often responsible for motion sickness, discomfort, or loss of balance. Because the SING IMT is integrated into the eye's internal optical system, it preserves the vestibulo-ocular reflex and ensures perfect stability of the retinal image during head movements, contributing to more stable and comfortable dynamic vision. Moreover, depth perception can be effectively exploited thanks to the anterior position of the nodal point of the implanted eye's optical system, which enhances motion parallax cues and improves spatial perception even in the absence of stereoscopic binocular vision.

The SING IMT is implanted in only one eye, leaving the other free to contribute to peripheral perception and mobility. The patient thus learns to manage visual attention flexibly, using the implanted eye for tasks requiring detailed vision and the fellow eye for orientation and navigation. This functional alternation between the two eyes, known as biocular multiplexing, results in overall improvement in autonomy and performance in everyday life, with better adaptability to different visual contexts.

In addition to functional and perceptual advantages, the SING IMT also introduces important innovations at the surgical level. The device features a preloaded delivery system that allows implantation through reduced incisions, between 6.5 and 7.5 mm, making the procedure safer, less invasive, and suitable for outpatient settings. The implantation process is faster than previous versions and involves cataract removal via phacoemulsification, followed by insertion of the glass telescope integrated into a silicone support within the capsular bag. This technical evolution not only reduces operative time and risks but also improves postoperative comfort and visual recovery quality (3–4).

B0004 – Who can decide and use the new technology?

The decision to use the SING IMT technology must result from a careful multidisciplinary clinical assessment involving both the patient and a highly specialized medical team. This integrated approach is essential to ensure an informed choice based on rigorous clinical criteria and a personalized functional evaluation.

The device is indicated for patients aged 55 years or older with severe or profound visual impairment (corrected distance visual acuity between 20/160 and 20/800) caused by end-stage AMD. In particular, this refers to advanced forms of the disease characterized by geographic atrophy or a disciform scar involving the fovea. This condition must also be accompanied by a visually significant cataract.

To be eligible for SING IMT treatment, the patient must meet all required clinical and functional criteria. First, they must be willing to participate in a preoperative preparation program, which includes an evaluation by low-vision specialists and the use of an external telescope. This tool allows the patient to realistically experience the visual effects expected from the implant, enabling an informed and conscious decision. During this process, the patient must demonstrate a significant visual improvement, quantifiable as at least five letters on the ETDRS chart when using the telescope.

Another requirement concerns the fellow eye, which must retain adequate peripheral vision, essential for compensating for the reduction in central visual field that may occur in the implanted eye. Finally, the patient must commit to consistently following a postoperative visual rehabilitation program under the guidance of a low-vision specialist, with the aim of optimizing the use of the device in daily life (1–3).

The informational phase preceding the procedure plays a crucial role. The patient must receive detailed, clear, and easily understandable explanations regarding the characteristics of the device, the surgical procedure, and postoperative implications. The physician is responsible for illustrating the surgical steps, possible postoperative symptoms and discomfort, required precautions, and the importance of strict adherence to the therapeutic and rehabilitative pathway.

The NG SI IMT 3X device is supplied in sterile packaging, preloaded in a single-use delivery system contained within a sealed blister. An identification card, including essential data for implant traceability, is also provided. This card must be given to the patient, along with the

recommendation to keep it carefully and present it to any ophthalmic specialist consulted in the future.

Before surgery, the patient undergoes a series of diagnostic evaluations to confirm suitability for implantation. Among the essential assessments are corneal endothelial cell density and anterior chamber depth. The surgical procedure, performed under retrobulbar or peribulbar anesthesia, begins with pharmacological pupillary dilation using mydriatic agents. The eyelid speculum is then positioned, and the operating microscope is aligned to ensure optimal visualization of the surgical field (1).

Regulatory status

A0020 – For which indications has the new technology received authorization or the CE mark?

The SING IMT technology represents the evolution of the IMT system, which was already approved by the FDA in 2010, and obtained CE marking for the European Union in 2020, with certification issued by Notified Body 0483 (MDC Medical Device Certification GmbH) in accordance with Directive 93/42/EEC on medical devices. It is currently placed on the market as a “legacy device” pursuant to Article 120.3 of Regulation (EU) 2017/745.

The CE-marked indication concerns the treatment of patients with bilateral central scotomas due to end-stage AMD, with stable visual impairment ranging from moderate to profound (8–9).

Other

A0022 – Who produces the technology?

SING IMT is manufactured by Samsara Vision, Inc., a privately held medical device company (formerly known as VisionCare Inc.) specializing in the research, development, production, and commercialization of implantable ophthalmic devices. The company is committed to developing innovative solutions aimed at significantly improving the vision and quality of life of individuals affected by untreatable retinal diseases (8).

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SAF Domain Safety

Topic & Issue

Safety (SAF)

Table 6 – Topic & Issues Safety (SAF)

Topic	Issue	Assessment element ID
Patient safety	How safe is the technology compared to the comparator(s)?	C0008
	What are the susceptible patient groups most likely to be harmed by the use of the technology?	C0005

Patient safety

C0008 – How safe is the technology compared to the comparator(s)?

The available data, although still limited in sample size and long-term follow-up, allow for an articulated overview of the postoperative complications observed and how these implicitly or explicitly compare with other therapeutic solutions.

In the 2023 study by Toro et al., postoperative corneal edema occurred in more than one-quarter of patients within the first month after surgery, but resolved in most cases with standard medical treatment consisting of topical steroids and hypertonic drops. Only one case showed persistent edema beyond 30 days, which resolved by the second month. The most significant complications, though rare, included iris incarceration, prolapse, and atrophy, some of which required surgical management. Overall, 14 ocular adverse events were recorded in seven patients (29.17%), but no cases of endophthalmitis or retinal detachment were observed, nor device malfunctions or aborted surgical procedures (1). The complications and adverse events reported in this study are summarized in *Errore. L'origine riferimento non è stata trovata.*

Table 7 – Complications and adverse events from the Toro et al. (2023) study [1]

Event	Number	Treatment Administered
Eye complications		
Corneal edema within 30 days	7	Topical and hypertonic steroid eye drops
Transient hyphema within 30 days	2 (intraoperative); 1 (postoperative)	-
Iris incarceration	3	Surgical repositioning
Iris atrophy within 7 days	2	-
Increased IOP within 7 days, requiring treatment	1	Brinzolamide 1% and timolol 0.5% eye drops
Iris damage	1	-
Iris prolapse	1	Surgical repositioning
Ocular adverse events		
Inflammatory deposits on the device	3	Topical steroid eye drops
Distorted pupil	3	Iridoplasty during suture removal
CNV	2	Intravitreal anti-VEGF injections
Iris atrophy > 7 days after surgery	2	-
Pigment deposits on the device	2	-
Corneal edema > 30 days after surgery	1	Topical and hypertonic steroid eye drops
Iritis > 30 days after surgery	1	Topical steroid eye drops

CNV: *choroidal neovascularization*; VEGF: *vascular endothelial growth factor*; IOP: *intraocular pressure*; BSS: *balanced salt solution*. Unless otherwise indicated, data are expressed as number (percentage) of participants.

In the 2023 study by Mastropasqua et al., no intraoperative complications were reported. However, in the postoperative period, the most common adverse events included corneal edema in two patients, with persistence beyond one month in one of them despite topical steroid therapy. One patient reported postoperative diplopia. Three patients required YAG laser iridotomy for IOP management, and two of these required prolonged topical glaucoma therapy. One patient was eventually scheduled for surgical removal of the device due to 360° iris–device synechiae resulting in poor pressure control (2).

Savastano et al., in 2024, in a study focused on postoperative monitoring, observed no major adverse events within the first three months, with particular attention to IOP measurement, endothelial cell density, and correct device positioning assessed by OCT. However, the optical design of the SING IMT limited fundus visibility, making OCT necessary for macular evaluation (3). In the updated 2024 work by Toro et al., the incidence of persistent corneal edema after 30 days was specifically quantified as 22.9%. Complications included a variety of events such as iris damage, implant dislocation, and inflammatory deposits on the device. Eighty percent of these events resolved within six months thanks to pharmacologic or surgical interventions, although seven events (iris atrophy, device pigmentation, iris damage) did not resolve (Errore. L'origine riferimento non è stata trovata.) (4).

Table 8 – Complications and adverse events from the study by Toro et al. (2024) [4]

Event	Proportion ,% (n)	Treatment Administered	Problem resolution
Corneal edema starting 30 days after surgery	22,9 (8)	Topical medications	Yes
Iris atrophy starting 7 days after surgery	11,4 (4)	N/A	No
Transient hyphema lasting more than 30 days	8,6 (3)	BSS rinse	Yes
Iris incarceration	8,6 (3)	Surgical repositioning	Yes
Distorted pupil	8,6 (3)	Iridoplasty	Yes
Inflammatory deposits on the device	8,6 (3)	Topical medications	Yes
Increased IOP within 7 days requiring treatment	5,7 (2)	Topical medications	Yes
Choroidal neovascularization	5,7 (2)	Anti-VEGF injection	Yes
Pigment deposits on the device	5,7 (2)	N/A	No
Iris damage	2,9 (1)	N/A	No
Implant dislocation	2,9 (1)	Surgical repositioning	Yes
Iris prolapse	2,9 (1)	Surgical repositioning	Yes
Iritis starting 30 days after surgery	2,9 (1)	Topical medications	Yes
Uveitis	2,9 (1)	Topical medications	Yes

IOP: *intraocular pressure*; N/A: *Not applicable*

In a second 2024 study by Savastano et al., attention was focused on the surgical phase, reporting that strong adherence of the previous IOL to the posterior capsule required cutting the haptic in some cases, without negatively affecting the outcome. One case of late implant dislocation into the vitreous chamber was surgically resolved with scleral fixation. Three-month outcomes showed no significant differences in complication rates between in-the-bag and sulcus implantation, though the small sample size was acknowledged as a limitation (5).

In 2025, Adamo et al. documented an incidence of transient corneal edema (27.3%), successfully treated, along with isolated cases of iris incarceration and device pigmentation. However, a relevant finding was that 90.9% of patients reported blurred vision during the three months following implantation, with a negative impact on quality of life. In three cases (27.3%), device removal and replacement with a conventional monofocal IOL were required (6).

Finally, also in 2025, Savastano et al. reported that even in the absence of postoperative complications (such as ocular hypertension, lens tilt, or endothelial damage), some patients complained of double vision, difficulty walking, difficulty performing daily activities, and persistent visual haze. The subjective discomfort was severe enough to require device removal in

several cases, highlighting the importance of careful patient selection and preoperative evaluation of the patient's potential perceptual adaptation to the telescope's optical system (7).

Overall, while showing an acceptable safety profile in terms of intra- and postoperative complications, the SING IMT presents a non-negligible frequency of transient or residual adverse events, requiring careful selection of eligible patients and structured clinical follow-up, especially in light of the still limited long-term data.

C0005 – Which are the susceptible patient groups that are most likely to be harmed by the use of technology?

The patient groups most susceptible to potential harm from the use of the SING IMT device are those with specific ocular or systemic conditions that contraindicate implantation or compromise its effectiveness. First, patients with diseases affecting peripheral vision in the fellow eye, such as retinopathies, optic neuropathies, or bilateral retinal degenerations, are particularly at risk. Since the functional principle of the IMT relies on the implanted eye for magnified central vision and the non-operated eye for peripheral vision and spatial orientation, any impairment of peripheral function compromises postoperative visual adaptation and increases the risk of disorientation, falls, and reduced quality of life.

Patients with active or recently treated choroidal neovascularization (CNV), as well as those who have undergone CNV treatments within the previous six months, also represent a vulnerable group. The presence of neovascular activity may lead to unpredictable disease progression, undermining the potential benefit of the implant. Similarly, individuals with uncontrolled glaucoma, elevated IOP, or a history of steroid-responsive ocular hypertension are exposed to a high risk of worsening visual function due to the intervention's effect on aqueous humor dynamics and outflow. Clinical data confirm that, in some cases, synechiae have formed between the iris and the device, leading to increased IOP that was unresponsive to medical therapy and requiring device removal.

Patients with corneal abnormalities, particularly those with endothelial dystrophies such as guttata or with endothelial cell density below 1600 cells/mm², are also susceptible, as they are more prone to complications such as persistent corneal edema. This condition has been widely reported in the available literature and, if not adequately managed, may irreversibly compromise corneal transparency, potentially necessitating device removal or corneal transplantation. Patients with unfavorable ocular anatomy, such as a narrow iridocorneal angle (Shaffer grade < 2), axial length under 21 mm, or high refractive errors (myopia > 6.0 D or hyperopia > 4.0 D), should also be considered at risk, as these conditions increase the likelihood of intraoperative or postoperative complications such as implant dislocation, iris damage, or difficulty positioning the device.

Patients with a history of prior intraocular or corneal surgery, as well as those with zonular weakness, pseudoexfoliation, diabetic retinopathy, retinal tears, ocular inflammatory disease, retinal vasculopathies, optic neuropathies, or retinal detachment, are generally excluded from clinical studies precisely because of the increased risk of anatomical and functional failure of the implant. In addition, cognitive impairment or significant communication deficits may interfere with the patient's ability to understand rehabilitative instructions, participate in postoperative visual training, and adapt to the new mode of vision, thereby negating the potential benefits of

the intervention (1, 3, 8).

Finally, a category of patients has emerged who, despite not presenting objective ocular complications, develop marked subjective discomfort after implantation. Some report double vision, a persistent sense of “fog” in the visual field, difficulty walking, or difficulty performing daily activities, negatively affecting quality of life. In several cases, these symptoms have led to device removal despite the absence of structural adverse events (7). This highlights that even clinically eligible patients may develop poor subjective tolerance to the implant, making a thorough preoperative assessment essential, not only anatomical and functional, but also psychological and motivational.

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EFF Domain Clinical efficacy

Topic & Issue

Clinical efficacy (EFF)

Table 9 – Topic & Issues Clinical efficacy (EFF)

Topic	Issue	Assessment element ID
Morbidity	How does technology affect the symptoms and outcomes (severity, frequency) of the disease or health condition?	D0005
	What is the effect of technology on general health-related quality of life?	D0012
Health-Related Quality of Life	What is the effect of technology on disease-specific quality of life?	D0013
	Were patients satisfied with the technology?	D0017
Patient Satisfaction	What are the overall benefits and harms of technology on health outcomes?	D0029
Benefit-Harm Balance		

Morbidity

D0005 – How does technology affect the symptoms and outcomes (severity, frequency) of the disease or health condition?

Recent studies on the SING IMT device show a significant impact on visual function in patients with end-stage AMD, improving both symptoms and functional outcomes of the disease.

In the study by Toro et al. (2023), the mean anterior chamber depth (ACD) was comparable between the study eye and the fellow eye at baseline, 3.272 ± 0.8063 mm vs. 3.498 ± 0.9577 mm, and remained substantially unchanged at 1 and 3 months postoperatively, measuring 3.036 ± 0.6317 mm and 3.024 ± 0.6277 mm, respectively. Although a significant IOP reduction was observed in the operated eye at 3 months compared with baseline, no significant differences emerged between eyes at any timepoint, suggesting that the SING IMT exerts a short-term beneficial effect on IOP.

In terms of visual acuity (VA), mean CDVA was comparable between eyes at baseline, while at 1 and 3 months the study eye showed a significant improvement, with a mean gain of $+7.3 \pm 5.1$ letters at 1 month and $+14.9 \pm 7.1$ letters at 3 months ($p < 0.0001$). The fellow eye showed no relevant changes. By the third postoperative month, 70.8% of study eyes had gained ≥ 10 letters, 58.3% ≥ 15 letters, 25.0% ≥ 20 letters, and 8.3% ≥ 30 letters, while 75% of fellow eyes worsened or showed no improvement.

Near vision (CDNVA) also improved significantly in operated eyes, with a mean gain of 4.0 ± 2.65 Jaeger levels at 1 month and 7.7 ± 3.17 levels at 3 months ($p < 0.0001$). All study eyes improved by at least 2 Jaeger levels, and 33% gained ≥ 10 levels.

However, endothelial cell density (ECD) decreased significantly in the operated eyes, with a mean loss of $9.6 \pm 13.3\%$ at 1 month and $10.4 \pm 13.3\%$ at 3 months ($p = 0.0047$ and 0.0025 , respectively) (1).

Endothelial cell loss is also confirmed in the study by Mastropasqua et al. (2023), who observed a 12.6% ECD reduction at 6 months (from a baseline of 2488 [2248; 2874] to 2174 [1946; 2536]). In the same study, baseline BCDVA in the study eye was 1.00 logMAR (≈ 20 ETDRS letters), improving to 30 letters at 6 months (1.30 logMAR in fellow eyes), with a median gain of 10 letters. Five patients gained at least one ETDRS line, four gained at least two lines, two gained at least three lines, and one gained six lines, while only one patient showed a slight worsening of 5 letters due to progressive dementia.

BCNVA improved by -0.30 logMAR from a baseline of 0.90 logMAR, with all patients reporting enhanced near vision. ACD measurements, endothelium-to-implant distance (EC-IMTd) and endothelium-to-iris plane distance (EC-IPd), showed a slight postoperative decrease in EC-IMTd (from 2.69 mm to 2.52 mm) and an increase in EC-IPd (3.19 mm to 3.40 mm), indicating anatomical changes in implant position relative to the cornea and iris. Mean IOP decreased from 17.5 mmHg to 12.5 mmHg at 6 months (2).

The study by Savastano et al. (2024) confirms functional and qualitative effectiveness of SING IMT in a cohort of 11 eyes, showing a significant improvement in distance VA, from a preoperative mean of 13 letters to 24.64 letters at 1 month and 23.91 letters at 3 months (mean gain >10 letters, $p < 0.001$).

Near vision, initially immeasurable due to severe central scotoma, also improved markedly, with means of 50.91 letters at 1 month and 59.09 at 3 months ($p < 0.001$), demonstrating that the telescopic lens effectively projects images onto functional peripheral retinal areas (3).

In another study by Toro et al. (2024) involving 35 patients, baseline mean BCDVA was 1.52 ± 0.142 logMAR (~20/640 Snellen). After SING IMT implantation, distance VA progressively improved, with mean changes of -0.14 logMAR at 1 month, -0.27 at 3 months, and -0.29 at 6 months (all $p < 0.001$), reaching a final mean of 1.24 ± 0.197 logMAR (~20/360 Snellen). At 6 months, 51.4% of patients had gained ≥ 3 lines, while only one patient worsened due to implant dislocation.

Near vision improved substantially: at baseline only 28.6% could read at near distance, while after 6 months this proportion rose to 97.1%. Mean DCNVA improved from 0.82 ± 0.155 logMAR (~20/125 Snellen) to 0.49 ± 0.230 logMAR (~20/63), a gain of three lines ($p < 0.0001$). IOP remained stable (< 1 mmHg variation) and ACD showed no significant change. Endothelial loss was progressive and significant: -8.3% at 1 month, -9.9% at 3 months, and -11.4% at 6 months ($p < 0.05$), higher than in the fellow eye (4).

Consistent results were observed in the second 2024 study by Savastano et al., which included pseudophakic patients, typically excluded from standard indications. In this cohort, CDVA improved from 11.4 ± 7.2 to 28.2 ± 6.3 letters at 3 months, and NDVA from 37.6 ± 16.3 to 51.4 ± 20.5 letters, confirming tangible functional gains in both distance and near vision. All patients had shown preoperative improvement > 20 letters with ETS (External Telescopic System), accurately predicting postoperative success.

Surgically, only 2 of 5 patients received in-the-bag implantation; in the remaining 3, the implant was placed in the ciliary sulcus due to collapsed capsular bags. One case of late vitreous dislocation occurred at 1 month and was successfully managed with vitrectomy and scleral fixation. No significant increases in IOP, macular or corneal edema, or endothelial cell loss were observed. The absence of systemic adverse events and the high degree of subjective satisfaction indicate good tolerability even in complex patients (5).

The study by Sasso et al. (2024), in 11 patients with advanced AMD and bilateral geographic atrophy (mean age 77.5 ± 8.0 years), reported improvements at 24 weeks: reading acuity (RA) improved from 0.64 ± 0.26 to 0.45 ± 0.19 logMAR ($p = 0.0181$), and reading speed (RS) increased from 16.9 ± 11.4 to 30.9 ± 17.6 words/min ($p = 0.0057$). Fixation stability (FS) improved significantly after two rehabilitation sessions, with over 55% of patients able to maintain fixation for at least 15 seconds, a physiological threshold.

BCDVA increased from 12.5 ± 8.6 to 28.5 ± 7.4 letters ($p < 0.0001$), with 82% gaining at least 10 letters, underscoring the essential role of multidisciplinary rehabilitation in clinical success (6).

Finally, the study by Adamo et al. (2025), in 11 patients followed for 6.5 ± 2.4 months, showed a significant improvement in CDVA from 17.00 ± 9.74 to 26.00 ± 8.53 letters ($p = 0.008$) and an improvement in CNVA from 12.27 ± 4.36 to 8 ± 2.61 Jaeger levels ($p = 0.004$). Endothelial loss was modest at $4.8 \pm 5.5\%$ at 3 months ($p = 0.003$), with no clinical impact on corneal function (7).

In summary, SING IMT implantation has been shown to significantly improve both distance and near visual function, reducing the severity of visual symptoms associated with advanced AMD. The effectiveness of the technology appears to depend not only on the surgical procedure itself but also on the quality of rehabilitative support, confirming that the approach must be multidisciplinary and personalized.

Health-Related Quality of Life

D0012 – What is the effect of technology on general health-related quality of life?

The SING IMT technology represents a significant advancement in the treatment of advanced-stage AMD, a condition that profoundly affects patients' quality of life, particularly due to the loss of central vision, essential for everyday activities such as reading, recognizing faces, watching television, or moving independently.

Findings from Toro et al. (2023 and 2024), Sasso et al. (2024), and Adamo et al. (2025) consistently highlight the negative impact of AMD on quality of life and the potential contribution of implantable technologies in partially restoring visual function. These studies show promising anatomical and functional outcomes, such as improvements in reading ability and reading speed, which are recognized as important predictors of vision-related quality of life (1, 4, 6–7).

In contrast with these more recent findings, earlier clinical studies on the original IMT by Hudson et al. (2006) and Boyer et al. (2015) also used standardized and validated tools, such as the NEI VFQ-25, to directly measure health-related quality of life, showing clinically meaningful improvements in many subscales as early as 12 months (8–9). This strengthens the hypothesis that the functional benefits of the device may translate into a positive perceived impact for patients.

Overall, current evidence suggests that the SING IMT has significant potential to improve visual functioning and, indirectly, quality of life. However, additional prospective studies that systematically integrate validated instruments (e.g., EQ-5D, SF-36, NEI VFQ-25) are needed to more precisely quantify its effect on generic health-related quality of life.

D0013 – What is the effect of technology on disease-specific quality of life?

Patient-Reported Outcomes (PROMs)

Based on available evidence, implantation of the SING IMT has produced a positive and clinically meaningful effect on disease-specific quality of life in patients with severe low vision secondary to AMD.

In the 2024 study by Savastano et al., evaluation was performed using the Low Vision Quality of Life Questionnaire (LVQoL), a validated and widely used tool for assessing the functional impact of low vision on daily activities. In addition to providing an overall score, the questionnaire explores specific dimensions of patients' lives, including daily functioning (e.g., reading, watching TV, cooking), social interaction (recognizing faces, participating in community activities), and psychological adaptation to low vision.

Results showed a mean increase in LVQoL score from 60.5 ± 12.1 at baseline to 71.0 ± 13.5 at three months postoperatively, a statistically significant improvement ($p < 0.001$).

Individual patient data showed that all participants improved relative to baseline, with increases

ranging from +5 to +21 points. For example, the patient with the lowest preoperative score (45) improved to 53 at three months, while the patient with the highest baseline score (77) improved to 86. This indicates that both patients with more severe baseline limitations and those with relatively better preoperative function benefited from the procedure. Error. L'origine riferimento non è stata trovata. reports the LVQoL scores for each participant before surgery and at 1 and 3 months post-intervention.

Notably, improvements in LVQoL extended beyond strictly visual aspects and encompassed overall autonomy and the ability to reintegrate into daily and social activities. The authors report that patients subjectively described improvements in tasks crucial to quality of life, such as watching television, reading, and recognizing the faces of friends and family members.

The improvement in quality of life documented at three months aligns with the broader evidence base on earlier-generation IMT devices, which had already shown a positive and durable impact on quality of life. Long-term follow-up reported in other studies (1, 2, and 5 years) confirmed the stability of these benefits, with meaningful visual gains (≥ 3 lines of BCVA in 59.5% of eyes at 2 years) accompanied by persistent or further improved patient-reported visual function (3).

Table 10 – LVQoL score before and after surgery [3]

Patient	LVQoL pre-intervention	LVQoL 1 month post-intervention	LVQoL 3 months post-intervention
1	74	80	90
2	52	58	65
3	69	74	87
4	77	80	86
5	51	54	60
6	56	59	62
7	48	50	55
8	71	74	80
9	45	49	53
10	47	52	60
11	75	78	83

Long-Term Outcomes

In clinical studies on the IMT, long-term evidence (up to 60 months) shows that the functional gains observed in the first two years are largely maintained in the medium to long term. In the 60-month extension (IMT-002-LTM) described by Boyer et al., the population with available data (n = 63 at 60 months) maintained a clinically significant improvement in visual acuity: the mean BCDVA gain decreased from +3.2 lines at 24 months to $+2.41 \pm 2.69$ lines at 60 months (n = 76 subjects with long-term data), with 62% of patients retaining at least +2 lines at the final visit. This indicates substantial retention of visual benefits even after 5 years.

Age-stratified analysis highlights important considerations for patient selection: younger patients (65–<75 years) tended to maintain visual gains more effectively than those ≥ 75 years. At 60 months, the mean improvement was $\sim +2.7$ lines in the 65–<75 group vs. $\sim +2.1$ lines in the ≥ 75 group, and a higher proportion of younger patients retained ≥ 3 lines. This suggests that age at the time of implantation is a key prognostic factor for the likelihood of maintaining benefit at 5 years.

Although these results derive from studies on the previous IMT model rather than the SING IMT, they nonetheless provide essential insights for understanding the durability of benefits and introduce the main long-term efficacy outcomes (8).

Patient Satisfaction

D0017 – Were patients satisfied with the technology?

Patient satisfaction following SING IMT implantation is a complex topic involving multiple dimensions. On one hand, objective functional results are promising; on the other, not all patients reported subjective satisfaction with the device, and in some cases this led to its removal.

In the study by Sasso et al. (2024), the authors highlight that SING IMT implantation followed by a structured visual rehabilitation program produced significant improvements in reading performance, fixation stability, and corrected visual acuity. Most patients achieved clinically meaningful gains in reading speed and accuracy after only 4–5 rehabilitation sessions. None were lost to follow-up, and all adhered consistently to an intensive 6-month rehabilitation program. These results suggest good engagement and potential satisfaction, although the study did not include a direct, validated assessment of patient satisfaction (6).

However, in the study by Savastano et al. (2025), the authors describe three cases in which patients requested device explantation despite achieving objective visual improvements. Reasons included blurred vision, double vision, difficulty performing daily activities, and a persistent sensation of “visual fog” that compromised quality of life. Notably, despite the absence of clinical complications (e.g., capsular opacification or lens dislocation), subjective discomfort was significant enough to prompt removal of the device, after which patients reported improved overall visual perception and greater satisfaction, even though their visual acuity returned to pre-implantation levels (10).

These findings suggest that, although SING IMT has the potential to significantly improve visual function in patients with advanced AMD, patient satisfaction does not depend solely on measurable outcomes but rather on a combination of psychological, perceptual, and contextual factors. A careful preoperative evaluation of the patient’s ability to adapt to a “new way of seeing,” along with adequate training and continuous support, is therefore essential.

In conclusion, patient satisfaction strongly depends on personalized therapeutic planning, the quality of rehabilitation, and the clinical and psychological support provided.

Benefit–Harm Balance

D0029 – What are the overall benefits and harms of the technology on health outcomes?

Implantation of the SING IMT telescope represents an innovative rehabilitative strategy for patients with advanced AMD, offering significant improvements in central vision, reading ability, and functional independence. Functional gains also extend to the psychosocial sphere, with

increased perceived quality of life thanks to greater independence in daily activities and reduced feelings of isolation often associated with severe vision loss.

The surgical procedure, performed through a small corneal incision, has demonstrated a generally favorable safety profile. Postoperative complications are limited and include, in some cases, a temporary increase in intraocular pressure and endothelial cell loss that tends to stabilize over time. Successful outcomes largely depend on proper patient selection and a personalized rehabilitation pathway, which is crucial for enabling functional reorganization and effective adaptation to the new visual system.

However, not all patients achieve the expected or desired outcomes. In cases of persistent dissatisfaction, device removal is indeed possible.

In conclusion, the SING IMT represents a promising therapeutic option for selected patients with advanced AMD, combining technological innovation with targeted visual rehabilitation. Nonetheless, it requires careful preoperative evaluation and personalized postoperative support to maximize benefits and manage potential challenges.

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ECO Domain

Costs and economic evaluation

Topic & Issue

Costs and economic evaluation (ECO)

Table 11 – Topic & Issues Costs and economic evaluation (ECO)

Topic	Issue	Assessment element ID
Resource Utilization	What types of resources are used during the provision of the evaluated technology and its comparators (identifying resource use)?	E0001
	What quantities of resources are used during the provision of the evaluated technology and its comparators (measuring resource use)?	E0002
	What are the measured and/or estimated costs of the evaluated technology and its comparators (evaluating resource use)?	E0009
	How does the technology change the need for other technologies and resource use?	D0023
Outcome Measurement and Estimation	What are the measured and/or estimated outcome(s) in terms of the health of the evaluated technology and its comparator(s) (identification, measurement, and evaluation of outcomes)?	E0005
Cost and Outcome Analysis	What are the estimated differences in costs and outcomes between the technology and its comparators?	E0006
Characterization of Heterogeneity	What are the uncertainties surrounding the costs and economic evaluations of the technology and its comparators?	E0010

Resource Utilization

E0001 – What types of resources are used during the provision of the evaluated technology and its comparators (identifying resource use)?

The rising incidence of AMD, particularly in its advanced forms, represents one of the most significant challenges for health systems in countries marked by pronounced demographic aging. In this context, technological innovation in ophthalmology offers a crucial opportunity to improve the quality of life of patients who experience a progressive and often irreversible loss of central vision. Among the emerging solutions, the SING IMT device stands out as a concrete option for restoring visual autonomy in individuals with few remaining therapeutic alternatives.

The resource-use analysis is conducted both from the perspective of the National Health Service (SSN) and from a societal perspective. It examines the costs associated with the technology under evaluation and with the comparator represented by the CSC (Table 12). The resources considered include direct healthcare and non-healthcare components, as well as indirect components related to the functional impact of low vision and blindness, thus coherently reflecting both perspectives. The adopted comparator reflects current clinical reality in late-stage advanced AMD, for whom no approved or routinely implemented intraocular treatment exists that can restore central magnified vision. In these patients cataract surgery, while often clinically relevant, does not address the underlying retinal functional deficit.

For the implementation of SING IMT, the evaluative scope includes the cost of the telescopic prosthesis, the costs of the surgical procedure determined by the per-minute operating room cost multiplied by the specific operative time, and the expenses related to the surgical team, materials, and anesthesia. This is complemented by functional rehabilitation, with particular attention to occupational therapy for sensory integration over six months, with one-hour-and-thirty-minute sessions twice weekly. The combination of implantation and rehabilitation defines the total implementation costs of SING IMT. The cost of the technology was derived from a rapid HTA report by the Tuscany Region[1], literature sources [2,3] and the national outpatient tariff system [4].

The follow-up phase includes the valuation of the cost of ophthalmologic visits and the number of monitoring visits during the first four years after SING IMT implantation, distinguishing between the first year and subsequent years, as well as the definition of control activities expected after standard cataract surgery. To estimate resource use and costs in the Italian clinical context, a survey was administered to clinicians experienced in the use of SING IMT, with the aim of detailing the follow-up pathways specific to this patient population.

In addition to direct healthcare costs, also direct non-healthcare expenses were included which, although not strictly clinical, are essential for the daily management of visual disability. Particular attention is given to the costs associated with low vision and blindness, including a one-time cost at the moment of transition to blindness and recurring costs differentiated by severe and moderate visual impairment. To adapt these cost items to the Italian context, a dedicated clinician survey was conducted; the annual recurring cost per patient related to care and social support needs was identified through Italian literature [5].

Finally, the analysis includes the costs of adverse events, including, when applicable, the costs related to the cataract surgery, valued using DRG tariff 13.41 – Cataract surgery without intraocular lens implantation (including preoperative visit, follow-up visits, and biometry), as well as the costs associated with the management of adverse events other than explantation, also estimated through the survey (additional visits, treatments, and procedures).

Table 12 – Cost drivers

Topic	Media	95% CI Lower	95% CI Upper	Source
Costs - SING IMT				
Cost of telescope prosthesis	€ 20.000,00	€ 15.000,00	€ 25.000,00	Report HTA Regione toscana [1]
Operation cost per minute	€ 25,98	€ 19,49	€ 32,48	Rossitto et al (2016) [2]
Occupational therapy sensory integration (6 months × 1-hr an 30' visits × 2)	€ 265,99	€ 199,49	€ 332,48	Sasso et al (2024) [3]
Costs – Visits				
Cost of ophthalmologist visit	€ 16,90	€ 12,68	€ 21,13	Lista tariffe ambulatoriali [4]
Costs of visual impairment and blindness				
One-off cost once patient develops blindness	€ 200,55	€ 150,41	€ 250,69	Expert opinion survey
Annual cost per patient	€ 16.283,06	€ 12.212,29	€ 20.353,82	INPS [5]
Severe visual impairment	€ 331,02	€ 248,26	€ 413,77	Expert opinion survey
Moderate visual impairment	€ 173,96	€ 130,47	€ 217,44	Expert opinion survey
Costs of adverse events				
Cataract surgery	€ 806,30	€ 604,73	€ 1.007,88	Lista tariffe ambulatoriali [4]
Adverse events (other than explantation)	€ 524,21	€ 419,37	€ 629,05	Expert opinion survey

E0002 – What quantities of resources are used during the provision of the evaluated technology and its comparators (measuring resource use)?

The measurement of resource use was conducted by quantifying activity volumes and the actual durations associated with the implantation of the SING IMT and with CSC (Errore. L'origine r iferimento non è stata trovata.). For the implementation of SING IMT, resource consumption was expressed in operating room minutes (specific surgical time multiplied by the cost per minute) [6].

The follow-up phase was measured in terms of the number of scheduled ophthalmology monitoring visits during the first year and up to the fourth year thereafter, explicitly distinguishing the follow-up profiles expected for SING IMT from those for patients undergoing standard cataract surgery/CSC. The frequency of controls and any ancillary procedures (e.g., instrumental examinations) were collected through a survey of expert clinicians to reflect current Italian practice.

In the context of wet AMD, the use of pharmacological resources was quantified as the number of ranibizumab administrations during the first year and in subsequent years according to the Summary of Product Characteristics [7], together with the corresponding schedule of monitoring visits in the initial year and from the second to the fourth year, in order to capture both therapeutic intensity and the clinical surveillance burden, as reported in the literature [8] [8].

Finally, resource use for adverse events was measured by quantifying the required healthcare services (additional visits and cataract procedures, when applicable), based on survey data and valued using national tariffs.

Table 13 – Resources used

Topic	Mean	95% CI Lower	95% CI Upper	Source
Costs – SING IMT				
Surgery time for SING IMT (minutes)	24,78	18,58	30,97	Grzybowski et al. 2020 [6]
Costs – Visits				
Number of monitoring visits first year - SING IMT	7,60	5,70	9,50	Expert opinion survey
Number of monitoring visits second year - SING IMT	3,60	2,70	4,50	Expert opinion survey
Number of monitoring visits third year - SING IMT	2,60	1,95	3,25	Expert opinion survey
Number of monitoring visits fourth year - SING IMT	2,00	1,50	2,50	Expert opinion survey
Number of monitoring visits per year - CSC	2,79	2,09	3,48	Expert opinion survey
Costs – Wet AMD				
Number of administrations of ranibizumab (first year)	3,61	2,71	4,51	Foglia et al (2017) [7]
Number of administrations of ranibizumab (after first year)	3,84	2,88	4,80	Foglia et al (2017) [7]
Number of monitoring visits per year (year 1)	9	6,38	10,63	McCarthy et al. 2019 [9]
Number of monitoring visits per year (years 2-4)	4	3,00	5,00	McCarthy et al. 2019 [9]

E0009 – What are the measured and/or estimated costs of the evaluated technology and its comparators (evaluating resource use)?

The analysis quantified the costs for the SING IMT technology and for the comparator in relation to the healthcare resources identified and their respective cost drivers. For the SING IMT technology, the following were measured or estimated: the price of the telescopic prosthesis, the cost of the surgical procedure valued as the cost per minute of operating room time multiplied by the specific operative duration (including surgical team, anesthesia, and materials), and the rehabilitation package consisting of sensory-integration occupational therapy over six months with twice-weekly 90-minute sessions. These components define the total implementation cost per patient.

Follow-up was quantified as the number of ophthalmology visits in the first year and in the subsequent years up to the fourth, with profiles differentiated from those of the comparator (standard cataract surgery/CSC). To reflect the clinical and care burden of the underlying condition, the analysis also included the costs related to wet AMD treatment with ranibizumab (cost per dose and number of administrations in the first and subsequent years), as well as the associated monitoring visits.

Costs linked to visual disability were also considered: a one-off cost at transition to blindness and recurring annual costs differentiated between moderate and severe impairment. Finally, the costs of adverse events were estimated as the required healthcare services (additional visits, cataract procedures, and, when applicable), based on national tariffs and organizational practice.

All costs are reported as euros per patient (one-off or annual) and aggregated by time horizon (year 1; years 2–4) and by NHS and societal perspectives, ensuring transparency and traceability of assumptions.

In addition, to position the economic value of the technology relative to CSC, the analysis was conducted within the Italian NHS using a Cost-Utility Analysis (CUA) [10]. The CUA compares the direct and indirect costs of the technology with outcomes expressed in quality-adjusted life years (QALYs), allowing a direct comparison between incremental costs and clinical/quality-of-life benefits for patients. The adoption of a CUA therefore provides a comprehensive view of the economic and clinical impact of SING IMT relative to its comparators, supporting decision-makers in assessing the financial sustainability and overall value of the technology and in guiding, in an informed manner, the allocation of resources towards interventions with the most favorable cost-utility profile in the national ophthalmology context.

D0023 – How technology changes the need for other technologies and the use of resources?

The introduction of SING IMT shifts the resource-use profile from a recurrent and fragmented reliance on low-vision support technologies to a focused upfront intervention (surgery + rehabilitation), with follow-up requirements that are generally more structured. In the short term, the technology increases the use of surgical resources (operating room time, surgical team, materials, anesthesia) and visuo-perceptual rehabilitation (sensory-integration occupational therapy), but in the medium/long term it may reduce and rationalize the number of low-vision-specific visits and contain part of the social costs by halting the progressive loss of vision.

Compared with Current Standard of Care (CSC), SING IMT does not replace disease-modifying treatments for the underlying condition (e.g., anti-VEGF for wet AMD when indicated), but it changes the intensity and type of monitoring required: more scheduled visits in the first year for adaptation and training, followed by follow-up focused less on assistive devices and more on maintaining performance with the implanted device. On the side of complications, the technology introduces specific adverse events (device-related) requiring dedicated resources, but it may at the same time reduce repeated use of low-/medium-value assistive technologies and social services linked to loss of autonomy. In summary, SING IMT reallocates spending, shifting from recurrent, diffuse consumption to a high-intensity upfront investment, with potential downstream de-escalation of other technologies and care resources as quality of life improves.

Outcome Measurement and Estimation

E0005 – What are the measured and/or estimated outcome(s) in terms of the health of the evaluated technology and its comparator(s) (identification, measurement, and evaluation of outcomes)?

The CUA compares costs with outcomes expressed in terms of utility (typically QALYs). In our comparison between SING IMT and CSC, health outcomes were identified, measured, and

translated into decision-useful metrics through a CEA/CUA framework: the primary outcome is QALYs, while Life Years (LYs) are reported as a secondary measure.

The efficacy inputs for SING IMT come from a prospective, multicenter, open-label study with the contralateral eye as control, which enrolled 217 patients (mean age 76 years) with bilateral end-stage AMD and central acuity between 20/20 and 20/400 [11,12]. Age stratification was performed (65–<75 years, group 1, n=70; ≥75 years, group 2, n=127), with follow-up extended to 60 months. The primary clinical efficacy outcome was improvement in BCDVA (ETDRS): at 60 months the mean gain was 2.41±2.69 lines (all patients, n=76), with 2.64±2.55 in group 1 and 2.09±2.88 in group 2; approximately 62% maintained ≥2 lines at 60 months, with better performance in younger patients. Quality of life measured using visual health-related PROMs (NEI VFQ-25) was also significantly higher in group 1 than in group 2.

Safety shows more frequent surgical complications in older patients (e.g., corneal edema >30 days: 7.1% in group 2 vs 4.3% in group 1); loss of ≥2 lines of BCDVA at 60 months occurred in 1/31 (3.2%) in group 1 and 3/32 (9.4%) in group 2; IMT removal occurred in 1.4% (group 1) and 7.9% (group 2). ECD showed an acute loss of ~20% at 3 months and a chronic rate of ~3%/year; cumulative loss at 60 months was lower in group 1 (35%) than group 2 (40%).

In the CUA model, these results are mapped into vision states (moderate impairment, severe impairment, blindness) with utility weights dependent on age/sex; utility decrements are applied for relevant adverse events (complications and device explantation). Gains in BCDVA and improvements in NEI VFQ-25 contribute to SING IMT QALYs, while progression trajectories and complications inform transitions and disutilities, allowing incremental comparison of SING IMT vs CSC within the NHS context.

Population

Errore. L'origine riferimento non è stata trovata. reports the characteristics of the study population. The model primarily adopts the characteristics of the cohort described in the IMT-002 study [13,14]. The baseline mean age is 76 years (95%CI: 75–77) [15], with the male proportion set at 48.8% based on Italian demographic sources [16].

Baseline visual status aligns with advanced-stage AMD: median ETDRS score of 25 letters (95%CI: 18.75–31.25; [15]), with baseline GA prevalence of 79.2% (95%CI: 59.4–99.0; [13]). Operational thresholds for visual-health states follow reference standards: legal blindness and moderate low-vision threshold set at 35 ETDRS letters (Visual Standards), with additional ICD-9/10 references for blindness definitions.

Table 14 – Demographic characteristics of patients included in the study

Topic	Media	95% CI Lower	95% CI Upper	Source
Age	76,00	75	77	Hudson et al. (2006) [15]
Proportion of male	48,80%	36,6%	61,0%	ISTAT [16]
Visual Acuity score at baseline	25	18,75%	31,25%	Hudson et al. (2006) [15]
Proportion of GA at baseline	79,2%	59,4%	99,0%	Toro et al. (2006) [13]
VA at legal blindness	35	NA	NA	Visual Standards

VA at blindness ICD-9, -10	20	NA	NA	Visual Standards
Odd ratio of premature mortality due to blindness	2,34	175,5%	292,5%	McCarty et al. 2019 [9]
Hazard ratio of premature mortality - moderate visual impairment	1,13	100,0%	141,3%	McCarthy et al. 2019 [9]
Hazard ratio of premature mortality - severe visual impairment	1,28	100,0%	160,0%	McCarthy et al. 2019 [9]
Eligible for cataract (CSC arm only)	100%	80%	-	Assumption
Percentage of recurrence of CNV	1,5%	1,1%	1,9%	Hamilton et al. 2018 [14]
VA threshold for moderate visual impairment	35	NA	NA	Visual Standards
Percentage of moderate impairment costs to blindness costs	31,00%	0,2325	0,3875	Survey
Percentage of severe impairment costs to blindness costs	19,00%	0,1425	0,2375	Survey

To reflect the impact of visual disability on survival, the model incorporates excess mortality risks associated with vision loss: odds ratio 2.34 for blindness, hazard ratios 1.13 for moderate low vision and 1.28 for severe low vision [8].

In the CSC arm, it is assumed that all of patients are eligible for cataract surgery (assumption based on clinical practice), while the annual recurrence rate of CNV is set at 1.5% [14], influencing progression toward worse vision states. Finally, for the societal perspective, cost relationships across vision states are parameterized by applying cost coefficients relative to blindness to scale annual costs associated with different levels of visual impairment. These percentages were derived through a survey of Italian experts, showing that 31.00% of patients have moderate low vision and 19.00% have severe low vision.

Markov model

A Markov model was adopted as the optimal structure to capture costs and health outcomes in patients with end-stage AMD treated with SING IMT. The model allows the estimation, for a simulated cohort of 1,000 individuals of aggregate costs and health outcomes and their comparison with those of a clinically comparable cohort following an alternative care pathway (CSC).

Model costs and health outcomes were discounted using an annual discount rate of 3%, in accordance with Italian guidelines [10].

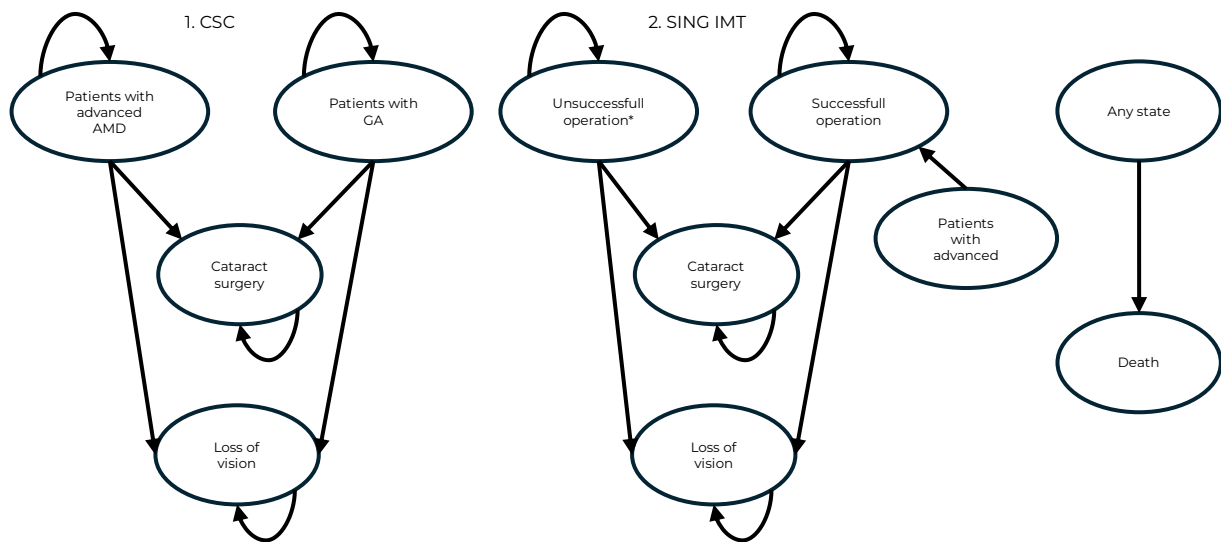
Each patient enters the model in one of the health states “Advanced geographic atrophy (GA)” or “Advanced wet AMD,” in both arms (SING IMT and CSC). In the CSC arm, a share of patients is eligible for cataract surgery, while the remainder follow the natural progression of AMD. In the SING IMT arm, the telescope is implanted in only one eye; patients may develop adverse events (AEs) that worsen outcomes by reducing quality of life [12] and increasing costs [4,17]:

- Explant within the first 2 years with a probability of 0.25% per cycle (95% Confidence Interval – CI: 0.19%–0.31%);
- Explant within the first 3 months with a probability of 4.39% per cycle (95% CI: 3.29%–5.49%), applied only to the first post-implant cycle;
- Explant up to 5 years with a probability of 0.49% per cycle (95% CI: 0.37%–0.61%), from the second cycle up to 60 months;
- Visual loss >2 BCDVA lines with a probability of 0.11% per cycle (95% CI: 0.08%–0.14%).

At any state, there is a persistent probability of death based on age-specific background mortality rates, which are incorporated into the model using ISTAT estimates [16]. The model runs on quarterly cycles, with transitions between states reflecting disease progression, treatment response, and the potential onset of AEs. **Figure 2** illustrate the patient pathway and the model structure for the CSC and SING IMT arms, respectively.

Because AMD has a substantial and long-lasting impact on quality of life, a lifetime time horizon was adopted to fully capture both the costs and the effectiveness of SING IMT over the entire course of the disease.

Figure 2 – Graphical representation of the Markov model for each strategy



GA: Advanced geographic atrophy; (*) Aborted or explanted intraocular lens

Efficacy

The clinical effectiveness of SING IMT was modelled using data from Boyer et al. 2015 [18] , which document the improvement in visual acuity over time in patients with advanced AMD, with an additional assumption extending the effect to 7 years (Errore. L'origine riferimento non è stata trovata.). The efficacy endpoint is expressed as the change in visual acuity (VA), measured in ETDRS letters, for each year following implantation; the duration of each effect is set at 12 months. Annual gains decrease progressively (17.5 → 16 → 14 → 12 letters), with the assumption of a plateau at 12 letters from the fourth to the seventh year.

Table 15 – Treatment effectiveness

Topic	Mean	95% CI Lower	95% CI Upper	Source
SING IMT efficacy				
Change in VA after 1st year	17,500			Boyer et al. 2015 [18]
Duration of treatment effect for first change (Months)	12,000	NA	NA	

Change in VA after 2nd year	16,000			
Duration of treatment effect for 2nd change (Months)	12,000			
Change in VA after 3rd year	14,000			
Duration of treatment effect for 3rd change (Months)	12,000			
Change in VA after 4th year	12,000			
Duration of treatment effect for 4th change (Months)	12,000			
Change in VA after 5th year	12,000			
Duration of treatment effect for 5th change (Months)	12,000			
Change in VA after 6th year	12,000			Assumption: extended outcome over 7 years
Duration of treatment effect for 6th change (Months)	12,000			
Change in VA after 7th year	12,000			
Duration of treatment effect for 7th change (Months)	12,000			
CSC efficacy – IOL				
Increase in VA for Cataract	3,400	0,640	6,160	Fooroghian et al. 2009 [19]

Utilities/disutilities for health states

The utility values used in the model are derived from the literature [11,12], quantifying vision-related quality of life across visual acuity categories (convertible to modelled vision states). Utility weights (0 = death; 1 = perfect health) are applied to each visual health state and form the basis for QALY calculations. A temporary disutility is applied for adverse events (AE) during the cycle in which the event occurs (or for the relevant duration) (Errore. L'origine riferimento non è stata trovata.).

Table 16 – Utilities

Topic	Media	95% CI Lower	95% CI Upper	Source
20/20 to 20/25	0,8900	0,8200	0,9600	Brown et al. 2000 [11]
20/30 to 20/50	0,8100	0,7300	0,8900	
20/60 to 20/100	0,5700	0,4700	0,6700	
20/200 to 20/400	0,5200	0,3800	0,6600	
Vision loss	0,4000	0,2900	0,5000	Brown et al. 2011 [12]
Disutility due to adverse events	0,0004	0,0003	0,0005	

Cost & Outcome Analysis

E0006 – What are the estimated differences in costs and outcomes between the technology and its comparators?

The SING IMT vs CSC analysis was conducted from both the NHS (SSN) and societal perspectives using CUA, which relates incremental costs (Δ Costs) to incremental quality of life (Δ QALY) to estimate the ICUR (Incremental Cost-Utility Ratio = Δ Costs/ Δ QALY). CUA quantifies the impact of SING IMT on QALY and, in descriptive terms, on healthy survival (LY).

In the absence of an official national threshold, results are interpreted against a reference willingness-to-pay (WTP) of €40,000/QALY, with alternative thresholds tested for robustness. SING IMT is considered cost-effective when the ICUR falls below the WTP.

Cost-Utility Analysis

Errore. L'origine riferimento non è stata trovata. presents the comparison of cost categories for SING IMT vs CSC.

Table 17 – Cost-effectiveness analysis – Deterministic results

	SING IMT	CSC	Incremental Δ	ICER
Cost of SING IMT	€ 20.909,72	€ -	€ 20.909,72	
AMD treatment & visit costs	€ 270,09	€ 47,66	€ 222,42	
Cataract	€ -	€ 806,30	- € 806,30	
Costs of explantation	€ 43,85	€ -	€ 43,85	
Costs of AEs	€ 837,31	€ -	€ 837,31	
Costs of visual impairment – Moderate	€ 941,25	€ -	€ 941,25	
Costs of visual impairment – Severe	€ 810,15	€ 941,63	€ 941,25	
Blindness	€ 12.148,38	€ 68.993,21	- € 56.844,83	
Total costs	€ 35.960,74	€ 70.788,80	- € 34.828,06	
Total life years lived	8,60	7,07	1,53	Dominant
Total QALYs lived	4,37	3,16	1,21	Dominant

The total costs of SING IMT are driven almost entirely by the initial investment for the device and implantation (€20,909.72), which represents approximately 90% of the overall cost. Additional cost components include the management of adverse events (€837.31) and potential explantation (€43.85), while follow-up costs remain limited (dry AMD visits: €191.72; wet AMD treatment/monitoring: €78.37). Costs related to visual disability are slightly higher in the SING IMT arm within the evaluated time horizon (moderate visual impairment: €941.25; severe visual impairment: €810.15). The total costs are of €83,128.36 per patient. Outcomes associated with the intervention amount to 8.60 life years and 4.37 QALYs.

In the CSC arm, spending is dominated by the cost of blindness (€68,993.21), to which are added dry AMD visits (€9.91), wet AMD treatment/visits (€37.75), cataract costs (€806.30), and costs associated with severe visual impairment (€941.63), for a total of €70,788.80 per patient. Outcomes for the comparator correspond to 7.07 life years and 3.16 QALYs.

The differential analysis shows a gain in favor of SING IMT of +1.53 life years and +1.21 QALYs. The strategy is cost-saving and that indicates that SING IMT dominates CSC (better outcomes at lower cost over the analysed horizon). This result remains consistent with the reference willingness-to-pay threshold (€40,000/QALY) and reinforces the conclusion that the technology is cost-effective within the Italian NHS.

From the NHS perspective, the Incremental Net Monetary Benefit (NMB) is €27,073.02. and €83,917.85 if the social perspective is considered, with the inclusion of indirect and social costs. Considering a willingness-to-pay threshold of €40,000 per QALY, the adoption of SING IMT generates a clearly positive net economic value compared with CSC. In other words, the monetized benefit of the additional QALYs gained with SING IMT more than offsets the cost difference between the two strategies. A NMB of this magnitude confirms not only the cost-effectiveness of the intervention, but also its substantial economic attractiveness for the NHS.

Heterogeneity characterization

E0010 – What uncertainties surround the costs and economic evaluations of the technology and its comparators?

In the context of health technology economic evaluations, such as the cost–benefit analysis of SING IMT versus CSC, two main types of sensitivity analyses are commonly used to assess the robustness of the results: deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). Both methodologies are essential for addressing and quantifying the uncertainties that naturally surround the costs and economic assessments of new healthcare technologies, yet each adopts a distinct approach to uncertainty.

Univariate DSA, used in the CUA, allows exploration of how variations in specific input parameters influence the ICER. This approach provides a clear view of the impact that precise parameter changes can have on the total cost of the intervention, enabling decision-makers to identify which factors exert the greatest influence on overall costs. However, uncertainty is treated one dimension at a time, modifying a single parameter, meaning that potential interdependencies between variables may not be fully captured.

In contrast, multivariate PSA addresses uncertainties in a more complex and realistic way. In this analysis, all input parameters are varied simultaneously according to predefined probability distributions, reflecting the intrinsic uncertainty in cost data, clinical effectiveness outcomes, and other key factors. This approach generates a distribution of possible economic outcomes and provides a more holistic and probabilistic understanding of uncertainty. It helps assess the confidence that can be placed in the results and the likelihood that a technology is cost-effective compared with its comparators.

Both approaches, despite their differences, play a critical role in providing health decision-makers with the information needed to navigate the inherent uncertainty of economic evaluations. DSA offers immediate insight into the relative importance of different inputs in budget calculations, whereas PSA provides a comprehensive assessment of risk and variability. Both are essential for informed decision-making in a context of limited resources and evolving healthcare needs.

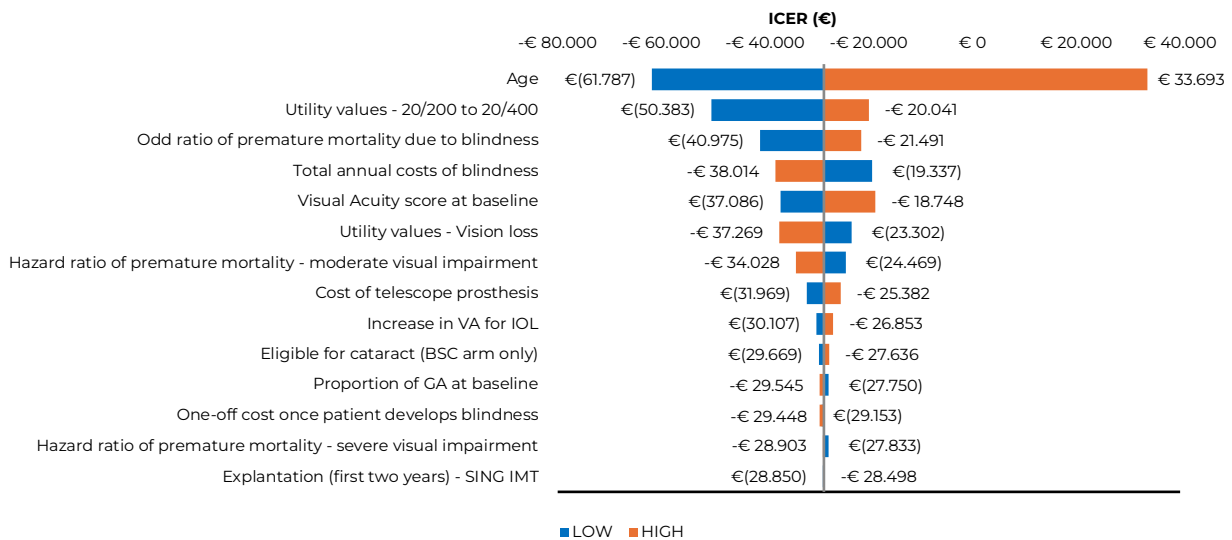
Deterministic Sensitivity Analysis

The deterministic sensitivity analysis (DSA) showed that model results are generally robust, with the ICER remaining negative across almost all one-way variations (**Figure 3**). Age is the only parameter capable of overturning this pattern: when age is varied across its plausible range, the ICER shifts from –€61,787 (low value) to +€33,693 (high value), indicating that higher age is associated with a higher, less favourable ICER.

For the remaining parameters, the ICER stays negative. Higher utility values for the 20/200–20/400 state and for vision loss, better baseline visual acuity, greater improvement in VA with IOL, and higher cost of the telescope prosthesis all shift the ICER towards zero (from about –€50,000 to –€18,000), thus slightly weakening the economic advantage of SING IMT. In contrast, increases in the odds or hazard ratios of premature mortality related to blindness or moderate visual impairment, higher annual costs of blindness, and a larger proportion of GA at baseline drive the ICER further into the negative range, reinforcing the cost-saving profile of SING IMT. Variations in all other cost and clinical inputs (cataract eligibility, one-off blindness costs, severe-impairment

mortality, explantation and other adverse events, surgery time and operating-room costs, occupational therapy, and ophthalmologist visits) have only marginal effects, with ICER values remaining tightly clustered around the base-case and consistently negative.

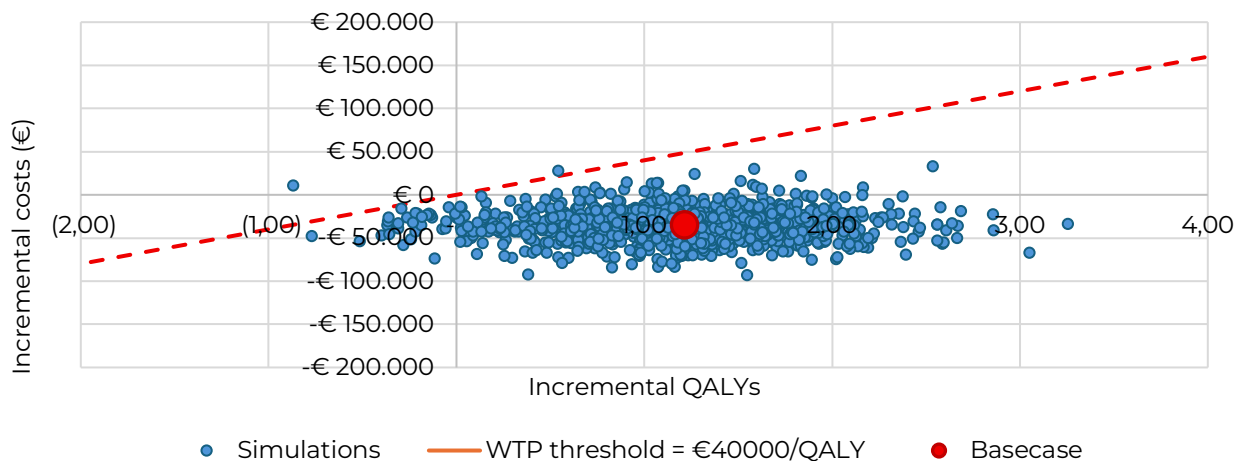
Figure 3 – Tornado plot



Probabilistic Sensitivity Analysis

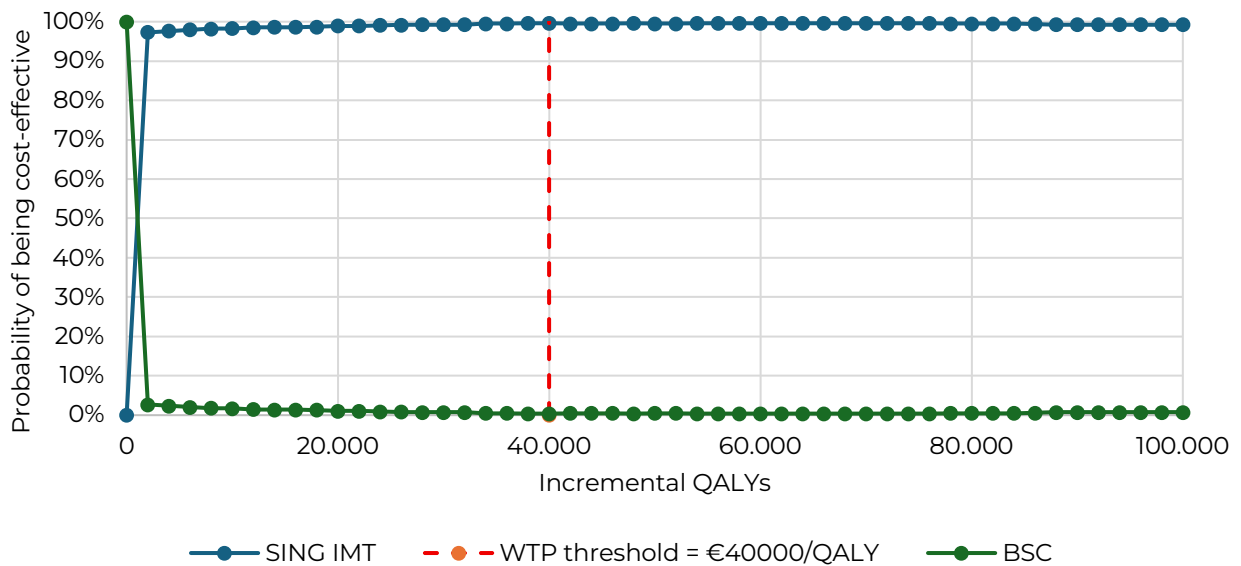
The probabilistic sensitivity analysis confirms the robustness of the base-case findings. As shown in the incremental cost-effectiveness plane (Figure 4), most simulations fall within the south-east quadrant, indicating that SING IMT is both less costly and more effective than CSC. The dispersion of points remains concentrated around negative incremental costs and positive incremental QALYs, consistently supporting the dominance of SING IMT. Only a very small proportion of simulations fall above the willingness-to-pay threshold of €40,000/QALY, represented by the orange line, and these do not alter the overall conclusion.

Figure 4 – Incremental cost-effectiveness plane



The cost-effectiveness acceptability curve shows that SING IMT has an extremely high probability of being cost-effective across the entire range of WTP thresholds (Figure 5). At the commonly accepted threshold of €40,000 per QALY, the probability that SING IMT is cost-effective is already very close to 100%, while CSC remains near 0% at all thresholds. The curve for SING IMT rapidly approaches 100% even at low WTP values, indicating that the intervention is overwhelmingly favored in probabilistic terms. These results confirm that, under virtually all plausible WTP thresholds, SING IMT dominates or strongly outperforms CSC, reinforcing the robustness and consistency of the economic evaluation.

Figure 5 – Cost-effectiveness acceptability curves



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ORG Domain

Organizational aspects

Topic & Issue

Organizational aspects (ORG)

Table 18 – Topic & Issues Organizational aspects (ORG)

Topic	Issue	Assessment element ID
Healthcare Delivery Process	How does technology impact current work processes?	G0001
	What type of patient flow is associated with the new technology?	G0100
	What type of engagement should be implemented for patients and caregivers?	G0002
	What process ensures adequate staff training and education?	G0003
	What forms of cooperation and communication regarding activities should be implemented?	G0004
Healthcare System Structure	What processes ensure patient/participant access to the new technology?	G0101
Process-Related Costs	What are the costs of the processes associated with the acquisition and installation of the new technology?	G0006
	How does the technology change the need for other technologies and the use of resources?	G0023
	What are the likely budgetary impacts of implementing the technologies being compared?	G0007
Management	What management issues and opportunities are associated with the technology?	G0008

Resource Utilization

G0001 – How does technology impact current work processes?

The introduction of innovative technologies, such as the new-generation intraocular telescope SING IMT, is a concrete example of how technology can profoundly transform work processes in healthcare. The study conducted at Policlinico Gemelli in Rome [1] shows that the introduction of this technology does not simply improve the patient's clinical condition but leads to a systemic redefinition of the operational and organizational modalities of the entire rehabilitation pathway. Implantation of the device requires close multidisciplinary collaboration between surgeons, orthoptists and visual rehabilitation specialists, generating new workflows that integrate skills that were previously separate.

The rehabilitation process is thus configured as a structured cycle in which the technology enables new forms of monitoring and performance assessment (e.g. through parameters such as reading acuity, reading speed and fixation stability). This objective approach introduces into work processes a logic of continuous outcome measurement, which guides clinical decision-making and enables incremental improvement of procedures. Moreover, postoperative management entails an intensive commitment both from healthcare personnel and from the patient, with the need for new skills and continuous updating in order to maximize the functional benefits of the device: teams must update rehabilitation protocols, including specific training to support the patient in the post-implant period so as to optimize functional results. This likely entails a redefinition of the skills required of therapists and rehabilitation professionals.

The study also suggests an evolution towards more flexible and digital modes of operation, through the introduction of rehabilitation via telemedicine, which would make it possible to overcome physical barriers and broaden access to rehabilitation services. This perspective reflects a broader transformation of work processes, oriented towards the connection between human skills and digital technologies. In this context, technology does not replace human activity, but becomes a catalyst for it, fostering collaboration, learning and organizational innovation.

G0100 – What type of patient flow is associated with the new technology?

The patient flow associated with SING IMT concerns individuals with advanced age-related macular degeneration [2]. Once eligibility has been confirmed, the process moves to surgical scheduling (usually as day surgery), followed by multiple postoperative follow-up visits to monitor implant stability and visual recovery. The standard pathway provides for up to 12 visual rehabilitation sessions with a low-vision specialist over a 12-month period [1].

A recent study on a first experience in pseudophakic patients (already operated for cataract), subjects who are not treatable with other pharmacological therapies and patients selected according to lesion severity and residual function show promising results [2]. The selection process requires strict control of inclusion criteria (advanced age, stability of the lesion, absence of concomitant disabling ocular pathologies, willingness to follow a post-implantation rehabilitation pathway) [1–2].

A recent study [1] enrolled 125 patients for the evaluation of SING IMT, illustrating a flow that starts from initial selection, continues through surgical implantation and culminates in functional reintegration via personalized rehabilitation training. The flow is characterized by close collaboration between ophthalmic surgeons, visual rehabilitation specialists and clinical-care coordination professionals, with constant monitoring of functional outcomes and quality of life.

G0002 – What type of engagement should be implemented for patients and caregivers?

The participant selection criteria clearly indicate that the success of the procedure depends not only on the surgical aspect, but also on the level of motivation and active participation of the patient. Candidates for implantation had to be “able, willing and motivated to follow a post-operative visual training and rehabilitation program” [3], confirming that the device’s effectiveness is closely linked to the patient’s readiness to undertake a structured visual adaptation pathway. This implies conscious and proactive involvement from the preoperative phase, including information on the benefits and limitations of the intervention, simulation of the optical effect using an external telescope and planning of a personalized rehabilitation program.

In the postoperative phase, the patient must assume a central role in the rehabilitation process, regularly attending visual training sessions and applying in daily life the strategies learned to maximize residual abilities and use of the new enlarged visual field. This requires active and continuous effort, which must be supported by appropriate therapeutic education and monitoring by the clinical team (ophthalmologist, orthoptist, visual rehabilitation specialist).

At the same time, the need for structured involvement of caregivers is emphasized. Patients with advanced macular degeneration are often elderly and functionally limited, so the presence of a caregiver is a crucial factor for the success of the pathway. The caregiver contributes not only logistical support (accompanying the patient to visits and managing postoperative home care), but also to daily rehabilitation, helping the patient carry out visual training exercises, manage environmental lighting and maintain motivation and confidence in the therapeutic pathway.

It is therefore desirable that the SING IMT implementation pathway include educational and informational sessions specifically dedicated to caregivers, so that they understand the nature of the intervention, the objectives of rehabilitation training and how they can facilitate continuity of care and the patient’s quality of life.

This engagement model is an essential condition for translating the potential functional improvement offered by SING IMT into an actual recovery of autonomy and quality of life for people with advanced macular degeneration.

G0003 – What process ensures adequate staff training and education?

The clinical and functional effectiveness of SING IMT implantation depends not only on the surgical act itself, but on the proper functioning of an integrated, multidisciplinary training process involving all healthcare staff engaged in the care pathway, from ophthalmic surgeons to orthoptists and visual rehabilitation specialists.

The study conducted at Policlinico Gemelli IRCCS in Rome [1] describes an SING IMT implementation model based on close collaboration between ophthalmic specialists, surgeons, orthoptists and visual rehabilitation professionals: the functional results (improvement in acuity and reading speed, fixation stability and increased BCDVA) were made possible precisely thanks to shared training and a structured operational protocol integrating surgical, rehabilitative and communication skills.

In particular, the process that ensures adequate staff training is articulated on three main levels:

- *Technical-specialist training for the surgical team:* SING IMT is a complex device that requires a highly standardized surgical technique, with reduced incisions (8 mm) and positioning of the telescope using a preloaded insertion system. All procedures described in the study were performed by a small group of experienced surgeons, following codified and reproducible procedures already published in previous studies. This implies the need for a specific training pathway for surgeons, focused on optical and biomechanical knowledge of the device, capsulorhexis and in-the-bag implantation techniques, and management of possible intraoperative complications (e.g. endothelial loss);
- *Rehabilitation training and orthoptic skills:* a distinctive element of this study is the extensive description of the postoperative rehabilitation program, designed and managed by the orthoptic staff at Gemelli. The protocol outlines a rehabilitation pathway structured into five areas of competence: visual skills, reading, writing, visuomotor integration and mobility. Each area is broken down into progressive steps, with targeted exercises (shape recognition, foveal centering, eye-hand coordination, reading with variable-contrast characters, etc.);
- *Communicative-relational training and pathway management:* a shared preoperative assessment, conducted by a multidisciplinary team, is crucial and includes not only clinical evaluation but also motivational, cognitive and social assessment. During the selection phase, patients were informed that the functional outcome of implantation does not represent a return to previous vision, but a new form of functional vision that requires a substantial investment of effort and time. This implies that clinical staff must be trained to communicate in a realistic and empathetic way, managing the expectations of patients and families and supporting their adherence to the rehabilitation pathway.

Training must therefore also include modules dedicated to effective communication and helping relationships, essential tools to support compliance and the success of the program.

G0004 – What forms of cooperation and communication regarding activities should be implemented?

The literature and specialist documentation recommend formalizing multidisciplinary teams composed of ophthalmic surgeons, nurses, visual rehabilitation therapists, psychologists and administrative staff, who collaborate in patient selection and care, jointly planning every phase from diagnosis to rehabilitation. Regular team meetings, multidisciplinary briefings/interviews and clinical-organizational meetings are recommended in order to update protocols, share

complex cases, evaluate functional outcomes and address any critical issues emerging along the pathway [1].

The SING IMT pathway requires the creation of shared documentation (multidisciplinary electronic medical records, follow-up reports shared between specialists and therapists, digital reminders) and continuous communication channels between clinicians, rehabilitation professionals and caregivers to monitor adherence, progress and emerging patient needs. Effective external communication tools aimed at patients and caregivers are also suggested, such as information leaflets, dedicated web platforms, counselling sessions, educational activities and webinars, to ensure full transparency and active participation of all those involved.

At organizational level, the dissemination of best practices and clinical results is based on national and international collaborative networks, with data sharing, audits between pilot centers, conference meetings and support networks developed by the manufacturer, ensuring continuous updating and mutual validation of adopted protocols. Centers are encouraged to participate in multicenter studies and clinical trials, with timely communication of results and innovations both within the clinical network and to the wider scientific community [1]

G0101 – What processes ensure patient/participant access to the new technology?

The process of accessing treatment with SING IMT is structured in several phases that ensure a safe and well-organized pathway for the patient. First, a preliminary clinical assessment is carried out, during which patients undergo an in-depth diagnostic work-up. This includes detailed eye examinations, analysis of functional visual loss and screening aimed at excluding ocular conditions that could be incompatible with device implantation.

The next step is candidate selection, which involves a rigorous screening process based on clinical, epidemiological and technical feasibility criteria. The objective is to identify patients who can derive maximum benefit from SING IMT, thereby ensuring appropriate therapeutic indication.

Once eligibility has been confirmed, the process moves to the information and consent phase, during which educational sessions are organized for both patients and their caregivers. These sessions explain expected benefits, potential risks and alternative treatments, as well as the details of the procedure and the possibility of failure. At the end of the information process, written informed consent is obtained.

This is followed by the planning and scheduling phase: once suitability has been approved, the surgical procedure is organized and the pre- and postoperative support pathway is defined. This includes training in device management, dedicated counselling and psychological preparation, all of which are fundamental to optimizing the surgical outcome and functional recovery.

In some healthcare settings, fast-track pathways are established at centers of excellence to facilitate access, ensuring a high standard of care and full adherence to clinical recommendations. After implantation, follow-up and monitoring begin, with systematic multidisciplinary check-ups to evaluate the effectiveness of the intervention, proper device integration and improvement in visual function.

Finally, patient engagement is a key element throughout the pathway. Ongoing education, psychological support and personalized counselling help promote adherence to treatment and maintain over time the benefits achieved through implantation [2].

G0006 – What are the costs of the processes associated with the acquisition and installation of the new technology?

The costs of the processes associated with the acquisition and installation of SING IMT include primarily the price of the device, the cost of the surgical procedure, staff training and postoperative rehabilitation expenses.

SING IMT is an advanced medical device with precision micro-optics and a minimally invasive implantation system; its unit cost is high compared with traditional ophthalmic devices, placing it in the upper market range for ocular prosthetic technologies. In Italy and other European countries, device procurement is subject to public tender procedures with specific requirements that assess cost in relation to the quality and safety provided.

Procedure-related costs include surgical and anaesthetic expenses, use of the operating theatre and hospital stay, which in the case of SING IMT is reduced thanks to the minimally invasive technique and performance in day surgery.

Training of specialized healthcare staff involves theoretical and practical courses with certified trainers, whose organization requires dedicated investment for updates and technical support.

The postoperative visual rehabilitation pathway lasts several months and includes specialized training sessions with therapists, whose cost must also be factored into the total expenditure [1].

G0023 – How does the technology change the need for other technologies and the use of resources?

Implantation of the SING IMT miniature telescope provides a significant improvement in visual acuity in patients with advanced macular degeneration, reducing dependence on external visual aids such as magnifying lenses, external optical systems or digital magnification software. This leads to partial replacement or reduced use of these assistive technologies.

Functional improvement after implantation may lessen the need for repeated or additional therapeutic procedures (e.g. intravitreal pharmacological treatments), with resulting savings in the use of related medical and technical resources.

The introduction of SING IMT entails a reallocation of resources, with initial increases in costs and resources dedicated to specialist surgery, staff training and rehabilitation support, but potential medium- to long-term savings arising from reduced visual complications and increased patient autonomy.

Effective adoption of the device may also reduce hospitalizations or visits for visual problems related to macular degeneration, thus optimizing overall utilization of healthcare resources [1].

G0007 – What are the likely budgetary impacts of implementing the technologies being compared?

In the available scientific literature, the budgetary impacts of implementing SING IMT, compared with other ophthalmic technologies for macular degeneration, include both high initial costs and potential long-term savings and economic benefits.

The introduction of SING IMT entails high upfront costs due to the device itself, specialized surgical intervention, staff training and postoperative visual rehabilitation programs.

These costs generally exceed those associated with less invasive or more conventional technologies or treatments, such as external visual aids or repeated pharmacological therapies.

Economic evaluations show that SING IMT can lead to significant improvements in patients' quality of life and autonomy, reducing the need for repeated treatments, additional medical visits and intensive care, with consequent savings in healthcare resources. Evidence indicates that the cost per quality-adjusted life year (QALY) gained with SING IMT is competitive with other therapeutic options, suggesting a favorable cost-effectiveness profile [4].

Compared with less innovative technologies or procedures, investment in SING IMT is justified by a sustained improvement in visual performance and overall patient well-being, leading to a reshaping of costs along the continuum of care.

G0008 – What management issues and opportunities are associated with the technology?

The introduction and management of the SING IMT device entail a series of challenges, but also important development opportunities for the healthcare system and for centers that adopt it.

From a management perspective, one of the main critical issues concerns surgical complexity and the need for specialist training. SING IMT implantation requires highly qualified staff and specific technical preparation, which may represent an initial barrier to adoption. This necessitates substantial investment in training and professional development programs, which are essential to ensure the safety and effectiveness of the intervention.

Another challenge concerns management of the rehabilitation pathway. After implantation, the patient must follow a complex and structured visual rehabilitation program, requiring careful coordination between surgeons, visual rehabilitation therapists and caregivers. While such multidisciplinary interaction is essential for treatment success, it increases organizational complexity and requires careful resource planning.

From a clinical standpoint, although SING IMT maintains an overall favorable safety profile, it requires constant monitoring and management of potential complications. Any issues, such as corneal endothelial changes or ocular inflammatory processes, must be identified and treated promptly, necessitating strict monitoring procedures and continuous follow-up.

Finally, the issue of accessibility represents another management challenge. The high cost of the device and the need for highly specialized facilities may limit the diffusion of the technology, creating territorial inequalities and reducing access opportunities for patients in some geographical areas.

However, alongside these critical issues, adoption of SING IMT offers significant managerial and clinical opportunities. First, the technology provides a substantial improvement in quality of life for patients with advanced macular degeneration, restoring partial visual capacity and greater autonomy in daily activities. This benefit also extends to caregivers, who experience a reduced care burden.

From a strategic perspective, the introduction of SING IMT can foster innovation and technological leadership, enabling healthcare facilities that use it to position themselves as centers of excellence in the treatment of advanced ocular diseases. This recognition may translate into greater patient inflow, development of new specialist skills and enhancement of human capital.

Implementation of this technology also promotes the development of integrated, multidisciplinary organizational models based on collaboration among different medical and rehabilitative professionals. This not only improves the quality-of-care pathways but can also increase the overall efficiency of the system [2].

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ETH, LEG & SOC Domains **Ethical, legal social analysis**

Topic & Issue

Ethical analysis (ETH)

Table 19 – Topic & Issues Ethical analysis (ETH)

Topic	Issue	Assessment element ID
Risk-benefit ratio	What are the benefits and the known or estimated risks for patients in the case of implementation or non-implementation of the technology?	F0010
	What are the benefits and risks associated with the use of the technology for family members, other patients, organizations, commercial entities, society, etc.?	F0010
Autonomy	Is the technology used for particularly vulnerable individuals?	F0005
	Does the implementation or use of the technology affect the patient's ability and opportunity to exercise their autonomy?	F0004
	Are specific interventions or supportive actions regarding information provision required in order to respect patient autonomy when the technology is used?	F0006
Justice and equity	How does the implementation of the technology affect the distribution of resources?	F0012
	Are there factors that could prevent a group or an individual from accessing the technology?	H0012

Risk-benefit ratio

F0010 – What are the known or estimated benefits and risks to patients if the technology is implemented or not implemented?

When assessing the ethics of implementing SING IMT in patients with end-stage AMD, it is essential to balance beneficence and non-maleficence [1-2]. On the one hand, the principle of beneficence requires that the intervention produce significant clinical and/or functional benefits in a population with high needs and limited residual options; on the other hand, non-maleficence requires minimising avoidable harm and suffering, especially when the intervention is invasive, requires lengthy rehabilitation, and may involve significant ocular complications. In this context, ethical judgement depends not only on average efficacy, but also on inter-individual variability in tolerability, the quality of candidate selection, the robustness of preoperative counselling, and the system's ability to ensure multidisciplinary follow-up.

Expected benefits in case of implementation

Available clinical evidence indicates that SING IMT implantation can result in clinically relevant functional improvements in central vision in patients with end-stage AMD. In several studies, distance vision improves significantly within a few months, with average gains in the order of +10–15 ETDRS letters and a substantial proportion of patients achieving an improvement of 3 lines or more. Near vision, which is often severely impaired or unmeasurable at baseline, can also improve substantially, with benefits for activities of high practical and relational value (reading, face recognition, use of digital devices).

A particularly relevant benefit, in ethical and clinical terms, is the possibility of regaining a degree of autonomy in a condition otherwise characterised by progressive dependence. The data show that, when the implant is integrated into a structured rehabilitation programme, improvements are observed in reading speed and accuracy and in fixation stability, with a potentially significant impact on activities of daily living. On a patient-centred level, the available PROMs show significant increases within three months, suggesting a perceived gain in terms of functioning and social participation.

Furthermore, as the SING IMT is an intraocular implant, it can offer a more stable and “natural” visual experience than bulky external aids, which are often poorly tolerated, and can reduce dependence on certain repetitive and fragmented assistive technologies. From this perspective, implementation can translate into an overall benefit that is not only clinical, but also existential and social: less isolation, greater agency, and a possible reduction in the burden on the carer (albeit after an initial period of intensive care).

Known or estimated risks in case of implementation

Alongside the benefits, implementation exposes patients to risks and discomfort that must be clearly explained and managed. The safety profile appears acceptable overall, but with a non-negligible frequency of adverse ocular events, some of which are predictable and manageable, while others are potentially persistent. Among the most frequently reported events are corneal oedema, inflammatory deposits on the device, complications affecting the iris, changes in

intraocular pressure and the need for additional procedures. An ethically sensitive issue is the loss of endothelial cells, observed significantly in the first few months, which requires careful selection and rigorous monitoring.

A particularly relevant clinical risk is the possible discrepancy between objective improvement and subjective tolerability. A minority but significant proportion of patients may report persistent blurred vision, diplopia, difficulty walking or performing activities of daily living (ADL); in some cases, this leads to device removal, sometimes even in the absence of objective complications. This data weighs heavily on the ethical balance: the risk is not only “biological” but also perceptual-functional, and translates into potential frustration, stress, loss of confidence and a deterioration in quality of life during the adaptation period.

These factors make the following ethically indispensable: (i) realistic preoperative counselling, (ii) an assessment of perceptual adaptation capacity and cognitive/psychosocial conditions, (iii) a guarantee that the patient will have access to an adequate rehabilitation programme, without which the expected benefit may be significantly reduced.

Scenario of Non-Implementation

The non-implementation of the SING IMT would leave patients with end-stage AMD reliant on alternatives that are often poorly effective in restoring central visual function, particularly in cases of GA or disciform scarring. The standard of care may include anti-VEGF therapy when indicated (for wet AMD) and the use of low-vision aids; however, in many patients the overall burden remains high. This includes progressive loss of autonomy, difficulties in activities of ADLs, increased risk of social isolation, greater dependence on caregivers, and rising social costs associated with visual disability. From an ethical perspective, non-implementation may therefore be seen as a renunciation of an option that, in an appropriately selected subpopulation, could offer meaningful gains in autonomy and quality of life.

Overall Ethical Balance

Based on the consolidated evidence presented in the dossier, the benefit–risk balance of the SING IMT can be considered favorable in carefully selected patients and in settings capable of ensuring experienced surgery, structured rehabilitation, and multidisciplinary follow-up. However, adherence to the principles of beneficence and non-maleficence depends on specific operational conditions: rigorous patient selection, comprehensive information, appropriate management of expectations, rehabilitative support, and vigilant monitoring of complications.

Limitations of the Evidence and Need for Further Studies

It is nevertheless important to emphasize that the favorable ethical judgment regarding the implementation of the SING IMT is based on a body of evidence that is still evolving. Although the available results are overall promising, they largely derive from studies with limited sample sizes and short- to medium-term follow-up. Moreover, interindividual variability in functional outcomes and subjective tolerability suggests the presence of prognostic and adaptive factors that are not yet fully understood.

From an ethical standpoint, this implies that implementation of the technology should be accompanied by a principle of caution and an explicit commitment to the generation of further evidence. In particular, there is a need for:

- long-term prospective evaluations of the durability of visual benefits;
- more robust comparative studies (ideally multicenter) allowing systematic comparison with available alternatives;
- systematic integration of validated PROMs to better capture the real impact on quality of life and patient satisfaction;
- in-depth analyses of predictors of success and failure, including age, cognitive profile, perceptual adaptation capacity, and intensity of rehabilitation.

In the absence of such data, there is a risk of overgeneralizing benefits or underestimating rare or late adverse effects. Therefore, from an ethical perspective, adoption of the SING IMT should be conceived as a gradual, monitored, and adaptive process, preferably concentrated in highly specialized centers, with systems for systematic collection of real-world data and periodic outcome audits.

In conclusion, the SING IMT may be considered ethically acceptable and potentially beneficial in the current context; however, this judgment remains conditional on the generation of more robust future evidence and on the healthcare system's ability to integrate the technology within a framework of clinical responsibility, transparency of information, and continuous learning.

F0010 – What are the benefits and risks associated with the use of the technology for family members, other patients, organizations, commercial entities, society, etc.?

From a family and social perspective, the implementation of the SING IMT can generate significant benefits that extend beyond the individual patient. Improvements in visual function and autonomy in activities of daily living (such as reading, mobility, and face recognition) allow many patients with advanced AMD to reduce their dependence on caregivers, with a positive impact on the quality of life of the entire family unit. Family members may experience a reduction in caregiving burden, both in terms of time devoted to daily assistance and emotional stress related to managing severe visual disability. This effect is particularly relevant in informal care settings, which are common in the elderly population, where loss of patient autonomy often translates into a substantial burden for spouses or adult children.

However, certain indirect risks and burdens for families should not be overlooked. The SING IMT treatment pathway requires a substantial initial commitment, including multiple preoperative assessments, the surgical procedure itself, and a structured postoperative visual rehabilitation program. During this phase, caregiver support is often essential to accompany the patient to clinical visits and to support home-based rehabilitative training. In addition, in a minority of cases, the occurrence of persistent subjective effects (such as blurred vision, diplopia, or difficulties with perceptual adaptation) may lead to frustration and disappointment, with emotional repercussions for the family context as well.

From a societal perspective, the introduction of the SING IMT may help reduce, in the medium to long term, the overall burden of severe visual disability, which is associated with social isolation, increased risk of falls, depression, and institutionalization. Even a partial improvement in functional vision may promote greater social participation and prolonged maintenance of independence, with potential collective benefits in terms of reduced social and care-related costs associated with blindness.

From the perspective of healthcare organizations, the SING IMT presents both benefits and challenges. Among the benefits is the potential, over the long term, to rationalize the use of resources dedicated to severe low vision, by reducing repeated reliance on external aids, fragmented visits, and social support services. Moreover, adoption of the technology may foster the development of highly specialized multidisciplinary care pathways, strengthening the role of referral centers and promoting integrated care models across surgery, rehabilitation, and follow-up.

On the other hand, there are relevant organizational and managerial challenges. Implementation of the SING IMT requires highly trained surgeons, dedicated teams, and intensive rehabilitation programs, leading to an initial increase in organizational burden and costs. Concentration of the technology in a limited number of centers of excellence may also generate inequalities in access, particularly for patients living in less well-served geographic areas, with potential ethical implications in terms of equity.

In summary, the overall balance between benefits and risks for family members, organizations, and society appears generally favorable, provided that adoption of the SING IMT occurs in a selective, monitored, and responsible manner.

Autonomy

F0005 – Is the technology used for particularly vulnerable individuals?

The SING IMT is intended for a patient population that can be considered particularly vulnerable across multiple dimensions, especially clinical, functional, psychological, and social. The technology is indicated for individuals with advanced or end-stage AMD, a chronic and progressive condition that predominantly affects people aged ≥ 65 years, who are often already characterized by multimorbidity and age-related frailty.

From a clinical and functional perspective, these patients present with severe bilateral impairment of central vision, associated with central scotomas, reduced reading ability, difficulty recognizing faces, and loss of autonomy in activities of daily living. This condition exposes them to an increased risk of falls and social isolation, representing not only a health-related vulnerability but also a care-related one.

From a psychological and relational standpoint, the progressive loss of central vision has a significant impact on personal identity, self-esteem, and emotional well-being. Symptoms of anxiety, depression, and frustration are common, linked to the perception of loss of independence and fear of further deterioration. In this context, the proposal of an innovative technology such as the SING IMT may represent, on the one hand, a source of hope, but on the other hand also a potential source of stress if expectations are not adequately managed.

A further element of vulnerability concerns the perceptual adaptation required by the device. Implantation of the SING IMT does not restore “normal” vision but introduces a new mode of visual perception that requires an intensive process of rehabilitation and learning. Patients with reduced cognitive flexibility, mild cognitive impairment, or limited motivation may experience greater difficulty adapting, with a consequent risk of dissatisfaction.

Finally, vulnerability extends to the social and family dimension. Many elderly patients rely heavily on caregiver support, who become an integral part of the therapeutic and rehabilitative pathway. This makes it essential to consider not only the patient but also the support context in which the technology is implemented.

In summary, the SING IMT is used in a vulnerable population, for whom adoption of the technology requires an ethically attentive and responsible approach.

F0004 – Does implementation or use of the technology affect the patient’s ability and opportunity to exercise autonomy?

Implementation of the SING IMT can significantly affect the patient’s ability to exercise autonomy, both functionally and decisionally.

On the one hand, a clinically meaningful improvement in functional central vision allows many patients with advanced AMD to partially regain essential abilities for daily life, such as reading, face recognition, use of digital devices, and orientation in familiar environments. These gains translate into greater operational autonomy, reducing dependence on caregivers for basic activities and promoting a partial resumption of self-management in domestic and social life. In this sense, the SING IMT helps counter one of the most disabling effects of advanced AMD: the loss of personal independence.

At the psychological level as well, recovery of functional vision may strengthen the perception of control over one’s health condition and life plans. The possibility of resuming activities previously abandoned has a positive impact on self-esteem and motivation, elements closely linked to the exercise of personal autonomy.

On the other hand, the SING IMT is not a technology that can be self-managed by the patient. Its implementation requires a highly medicalized pathway, including rigorous clinical selection, a specialized surgical procedure, and a structured, long-term visual rehabilitation program. In particular, adaptation to the new mode of vision requires active and continuous engagement, but also a significant initial dependence on the healthcare team and caregiver support. During this phase, patient autonomy may be temporarily limited.

Moreover, the technology introduces a new form of vision that is not always perceived as immediately beneficial. In some cases, despite objectively positive clinical outcomes, subjective discomfort (such as blurred vision, diplopia, or difficulties with ambulation) may compromise the perception of benefit and, consequently, the patient’s sense of self-determination. This makes the preoperative phase of information and expectation management particularly delicate.

For these reasons, safeguarding autonomy in the context of the SING IMT cannot be understood solely as a functional outcome, but must be ensured primarily through:

- a thorough, realistic, and iterative informed consent process;

- active involvement of the patient in the implantation decision, including preoperative simulation with an external telescope;
- a continuous and dialogical relationship with the multidisciplinary team;
- rehabilitative and psychological support accompanying the patient throughout the progressive adaptation to the device.

In summary, although requiring a high level of clinical and organizational support, the SING IMT has the potential to strengthen the functional and personal autonomy of patients with advanced AMD in the medium to long term. This potential can be fully realized only if the technology is embedded within a personalized care pathway that recognizes autonomy as a dynamic process to be supported, rather than as a given precondition.

F0006 – Are specific informational interventions or support actions required in order to respect patient autonomy when the technology is used?

Respect for patient autonomy represents a central ethical requirement in the use of the SING IMT, given the complexity of the technology and the vulnerability of the target population. In this context, the process of information provision and consent cannot be limited to standard communication, but requires specific and structured informational interventions.

Unlike other routine ophthalmological procedures, the SING IMT does not restore “normal” vision; rather, it introduces a new mode of visual perception that entails potential benefits as well as functional trade-offs and a significant rehabilitative commitment. Therefore, informed consent must include a clear and understandable explanation of:

- realistic expected benefits, avoiding wording that may induce unrealistic expectations;
- risks and limitations of the technology;
- the indispensable need for an intensive and prolonged visual rehabilitation pathway, without which clinical benefits may be limited or not perceived;
- available alternatives, including non-surgical options (low-vision aids, digital supports) and the option of no intervention.

A particularly relevant informational element, already integrated into clinical practice, is preoperative simulation using an external telescope, which allows patients to directly experience the optical effects of the device. This strategy represents a genuine support action for autonomy, as it transforms abstract information into direct perceptual experience, facilitating more informed decision-making.

Given the advanced age of patients and the possible presence of frailty, it is also necessary to:

- use simple, non-technical language, possibly supported by visual and written materials;
- allow adequate time for reflection, avoiding rushed decisions;
- involve, with the patient’s consent, family members or caregivers, who play a key role in the postoperative pathway;
- actively verify understanding of the information provided (teach-back).

From an ethical perspective, informed consent for the SING IMT should be conceived as a dynamic process, unfolding over multiple encounters and remaining open to reconsideration up

to the immediate preoperative phase. This approach is particularly relevant in light of the variability of subjective outcomes and the risk, documented in the literature, of dissatisfaction even in the presence of objectively positive clinical improvements.

In summary, the use of the SING IMT requires specific informational actions to ensure full respect for patient autonomy. Only through transparent and personalized communication can truly free, conscious, and informed consent be ensured.

Justice and Equity

F0012 – How does implementation of the technology affect the distribution of resources?

A central ethical criterion in assessing adoption of the SING IMT concerns its impact on the equitable and efficient distribution of healthcare resources, in a context of increasing pressure on public budgets and rising prevalence of chronic degenerative diseases related to population ageing. In this scenario, introduction of a technology with high upfront costs requires careful evaluation not only of clinical effectiveness, but also of its capacity to contribute to responsible and sustainable use of collective resources [3–4].

Implementation of the SING IMT leads to a reallocation of resource consumption: in exchange for a significant upfront investment (device, specialized surgical procedure, and intensive visual rehabilitation), the technology has the potential to reduce, in the medium to long term, the fragmented and recurrent use of resources associated with advanced visual disability. In particular, improvements in functional vision may result in:

- reduced continuous use of low- or medium-value low-vision aids;
- fewer repeated visits devoted exclusively to management of low vision;
- potential containment of social and care-related costs linked to loss of autonomy, including home care support and caregiver burden.

Economic analyses conducted within the context of the National Health Service suggest that, over the time horizon considered, the SING IMT may be cost-effective and potentially dominant compared with the current standard of care, generating gains in quality-adjusted life years (QALYs) at lower overall costs. From a distributive ethics perspective, this implies that adoption of the technology does not inefficiently divert resources, but may instead help free resources that can be reallocated to other high-priority healthcare needs.

However, the impact on resource distribution is not organizationally neutral. The high level of specialization required for implantation and rehabilitation entails an initial concentration of resources in centers of excellence, with the risk of territorial inequalities in access. This raises a relevant ethical issue: in order for resource distribution to be equitable, implementation of the SING IMT must be accompanied by planning and governance policies that ensure transparent eligibility criteria and access proportional to clinical need, avoiding restriction of benefits to privileged contexts.

In summary, implementation of the SING IMT produces an overall positive effect on resource distribution, favoring a shift from widespread recurrent costs to a targeted investment with high clinical and social value. This ethical benefit, however, is conditional on the healthcare system's

ability to govern introduction of the technology in a planned, monitored, and equity-oriented manner, so that economic efficiency effectively translates into distributive justice.

H0012 – Are there factors that could prevent a group or an individual from accessing the technology?

Several factors may limit or hinder access to the SING IMT for specific patient groups, primarily of an organizational, territorial, clinical, and socio-economic nature.

First, access to the technology is strongly conditioned by the availability of highly specialized centers. Implantation of the SING IMT requires advanced surgical expertise, appropriate infrastructure, and the presence of multidisciplinary teams (ophthalmic surgeons, low-vision specialists, visual rehabilitation therapists). These requirements lead to a concentration of services in a limited number of centers of excellence, predominantly located in large urban areas or within research hospitals and highly specialized institutions. This may generate territorial inequalities, disadvantaging patients living in rural or peripheral areas, who must face long travel distances, high indirect costs, and greater logistical difficulties in accessing evaluation, surgery, and rehabilitative follow-up.

A second critical element concerns the stringent clinical eligibility criteria. The SING IMT is indicated only for patients with end-stage AMD, specific ranges of visual acuity, adequate peripheral function of the fellow eye, and willingness to undertake an intensive rehabilitation pathway. While these requirements are necessary to ensure appropriateness and safety, they may exclude frail patients with comorbidities, reduced perceptual adaptability, or cognitive limitations, even in the presence of significant clinical need.

Additional access barriers are socio-economic and family-related. The care pathway associated with the SING IMT requires prolonged commitment over time, with numerous follow-up visits and visual rehabilitation sessions. Elderly patients living alone, without a stable caregiver, or with limited economic resources may experience difficulties in managing travel, adhering to the rehabilitation schedule, or ensuring the continuity of care necessary for intervention success. In this sense, dependence on family support represents an implicit selection factor.

Finally, informational, cultural, and communicative barriers may affect access. The complexity of the technology and therapeutic pathway requires clear, gradual, and personalized communication. Patients with low health literacy, language barriers, or limited familiarity with innovative technologies may not fully understand the opportunities and limitations of the SING IMT, reducing the likelihood of appropriate referral or informed adherence to the pathway.

In summary, access to the SING IMT may be limited by:

- concentration of the technology in highly specialized centers;
- territorial inequalities;
- selective clinical eligibility criteria;
- socio-economic barriers and caregiver burden;
- informational and communication challenges.

These factors make careful governance of implementation necessary, including referral networks, transparent access criteria, logistical support, and structured informational pathways, in order to

ensure that a technology with high clinical value does not generate new forms of inequality in access to care.

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Topic & Issue

Social analysis (SOC)

Table 20 – Topic & Issues Social analysis (SOC)

Topic	Issue	Assessment element ID
Patient perspective area	What are patients' expectations and preferences regarding the technology, and what do they expect to gain from it?	H0100
	What is the burden on caregivers?	H0002
Communication-related issues	Which specific aspects may need to be communicated to patients in order to improve adherence?	H0203
Social group-related aspects	Are there patients who currently do not have adequate access to the available therapies?	H0201

Patient Perspective Area

H0100 – What are patients’ expectations and wishes regarding the technology, and what do they expect to gain from it?

At present, there are no specific studies in the literature addressing patients’ expectations and wishes regarding use of the technology in question, given its recent introduction into clinical practice. However, considering on the one hand the burden of disability and loss of independence associated with AMD, and on the other hand the potential for improvement achievable—provided there is a high level of clinical and organizational support (experienced surgery, structured rehabilitation [up to 12 sessions], multidisciplinary follow-up, and appropriate communication and educational support¹) it is desirable that dedicated studies be undertaken in this area.

Nevertheless, it is reasonable to assume that patients’ expectations are understandably high, as they are closely linked to the hoped-for recovery of vision and, consequently, to overall autonomy and the ability to reintegrate into daily and social activities (greater agency, reduced isolation, and a possible reduction in caregiver burden).

An indirect indication of this can be identified both in the attention devoted to training clinical staff in appropriate management of patient and caregiver expectations, as reported in the organizational domain of this report, and in an initial single-center cohort study [8], which describes three patients who requested explantation of the implanted device. The study reports that this request was motivated by the following symptoms: “double vision, difficulty walking, difficulty performing simple daily activities, and the presence of unbearable blurring in the visual field. Even in the absence of postoperative complications... the high level of discomfort and the resulting reduction in quality of life required removal of the device” [8]. Consequently, taking into account the technical characteristics of the technology, its current use in AMD, and its efficacy/safety profile, it appears crucial—when informing patients—to foster realistic expectations. As stated in the organizational (ORG) chapter of this report, “the functional outcome of implantation does not represent a return to previous vision, but a new form of functional vision that requires a significant investment of time and energy.”

This implies a rehabilitative pathway structured across specific areas of competence (visual skills, reading, writing, visuomotor integration, and mobility), which requires conscious, motivated, and proactive patient involvement, as reported in the available literature cited in the organizational domain of this report.

H0002 – What is the burden on caregivers?

AMD, particularly in its advanced forms, generates disability and loss of independence that require caregiver support (mainly spouses and adult children), who should be considered an integral part of the patients’ therapeutic and rehabilitative pathway.

Such support is also required in the immediate postoperative period and during rehabilitation, necessitating careful coordination among surgeons, nurses, rehabilitation therapists, caregivers,

¹ For further details, see the EFF and ORG chapters of this report.

and the patient. As stated in the organizational chapter of this report, “the need for structured involvement of caregivers is emphasized. Patients with advanced AMD are often elderly and functionally limited; therefore, the presence of a caregiver represents a crucial factor for the success of the pathway. The caregiver provides not only logistical support (accompanying patients to visits and managing postoperative home care), but also contributes to daily rehabilitation, helping the patient perform visual training exercises, manage environmental lighting, and maintain motivation and confidence in the therapeutic pathway.”

It is therefore desirable that “the SING IMT implementation pathway include educational and informational sessions specifically dedicated to caregivers, so that they understand the nature of the intervention, the objectives of rehabilitative training, and the ways in which they can facilitate continuity of care and the patient’s quality of life,” as well as the expected benefits, potential risks, therapeutic alternatives, procedural details, and the possibility of treatment failure.

The role of caregivers in the SING IMT pathway is particularly relevant because they, together with the clinical staff, should be included in ongoing communication channels aimed at monitoring adherence, postoperative clinical progress, and emerging patient needs.

Finally, it should not be overlooked that, insofar as the technology in question can significantly improve the quality of life of patients with AMD by restoring a degree of autonomy, this benefit also extends to caregivers in terms of a gradual reduction in caregiving burden, as well as reduced emotional and psychological stress associated with managing severe patient disability².

Communication-Related Issues

H0203 – What specific aspects may need to be communicated to patients in order to improve adherence?

Communication with patients (and caregivers) in the pre- and post-operative phases by the clinical staff (ophthalmic surgeons, nurses, and visual rehabilitation therapists) regarding SING IMT therapy should be characterized by accuracy, realism, and clarity, facilitating the responsible exercise of patient autonomy and the expression of informed, free, and voluntary consent and adherence to use of the technology³. It is also advisable to structure multidisciplinary teams both for internal team meetings and for encounters with patients and caregivers.

The issue of communication essentially concerns three categories of stakeholders:

1. The patient. The needs and preferences of patients eligible for SING IMT therapy relate, in general, to the uniqueness of each individual and, therefore, to the treating physician’s ability to build a “therapeutic alliance,” i.e., an effective helping relationship that requires a proactive role from the patient. Information and education should focus on:
 - the fact that use of the SING IMT shows a positive risk–benefit profile, subject to ongoing updates in light of periodic device-vigilance reports, as regulated by Ministerial Decree of 31 March 2022;

² For further details, see the ORG chapter of this report.

³ For further details, see the TEC and ETH chapters of this report and, for general aspects related to communication, see [9] National Bioethics Committee, Information and consent in medical practice (20.6.1992). In: <https://bioetica.governo.it/it/documenti/pareri/informazione-e-consenso-allatto-medico/> (accessed on 15.2.2026).

- comparison with other available treatments, providing an overview of therapeutic options and current healthcare recommendations;
 - the rigorous and continuous safety controls (laboratory studies, post-marketing studies) to which all medical devices are subject throughout their life cycle, in accordance with international and national regulatory standards, aimed at ensuring that devices are safe and effective before being used in patients and that appropriate measures are taken should serious adverse events occur;
 - the importance of supporting patients through educational and training programs, psychological support, personalized counseling, and external communication tools (see below) to help them manage treatment independently, thereby improving therapeutic adherence.
2. Caregivers. Alongside patients, caregivers should be recipients of both educational and training pathways (see H0002 – What is the burden on caregivers?) and external communication tools (e.g., informational brochures, dedicated web platforms, counseling sessions, educational activities, and webinars) aimed at ensuring full transparency and active participation of all involved parties.
 3. The wider community. Public awareness of the reality of AMD and the possibilities for its clinical management should be promoted and maintained through targeted social communication campaigns led by institutional bodies, in collaboration with patient associations.

Social Group-Related Aspects

H0201 – Are there patients who currently do not have adequate access to available therapies?

The principle of justice, grounded in the values of the National Health Service, in principle supports universal availability of effective and safe treatments for AMD, while at the same time pursuing organizational and economic–financial sustainability of healthcare services.

At present, as highlighted in the organizational chapter of this report, access to the technology may represent a critical issue, since “the high cost of the device and the need for highly specialized facilities—consequently requiring highly specialized surgical expertise and intensive rehabilitation programs—may limit the diffusion of the technology, generating territorial inequalities and reducing access opportunities for patients in certain geographic areas.”

Additional factors limiting access to the SING IMT may include:

- selective eligibility criteria for use of the technology which, while understandably prioritizing patients most likely to benefit, may risk excluding individuals with significant clinical need who have comorbidities, reduced perceptual adaptability, or cognitive limitations;
- socio-economic and family barriers, particularly affecting elderly patients who live alone or lack a stable caregiver. In practice, availability of family or caregiver support may represent an implicit negative selection factor;

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- informational, cultural, and communication barriers, or cognitive limitations affecting patients with low health literacy, language difficulties, or limited familiarity with innovative technologies.

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Topic & Issue

Legal analysis (LEG)⁴

Table 21 – Topic & Issues: Legal Analysis (LEG)

Topic	Issue	Assessment element ID
Autonomy	What legal requirements exist for providing adequate information to users or patients, and how should these be addressed when implementing the technology?	I0002
	Who can give consent for [minors and] incapacitated persons?	I0034
Ethical Aspects	Does the implementation or use of technology affect the realisation of fundamental human rights?	F0014
Authorisation and security	What authorisations and registrations does the technology have?	I0015
	What do laws/binding regulations require in terms of technology security, and how should this be addressed when implementing technology?	I0017

⁴Considering the continuous evolution that characterises both national and supranational legal systems, the considerations set out below are based on the content of the regulations in force at the date of drafting this report. In particular, the validity of the regulations cited was verified by consulting the Normattiva portal <https://www.normattiva.it/> for Italian regulations and the Eur-Lex portal <https://eur-lex.europa.eu/homepage.html> for regulations issued within the European Union.

Autonomy

I0002 – What types of legal requirements exist for providing adequate information to the user or patient, and how should they be addressed in the implementation of the technology?

Within HTA processes, analysis of legal aspects (LEGAL domain) aims to identify the legal issues raised by the development, implementation, and use of a given health technology, as well as to identify, in the circumstances considered, the rules designed to protect the rights of individuals and the interests of society as a whole [1, 2]. Legal analysis, in other words, makes it possible to define the boundaries of lawfulness within which the health technology under assessment may be offered in compliance with national and supranational regulations intended to safeguard a broad range of rights, including both public health and respect for individuals' psychophysical integrity and autonomy.

With specific regard to the respect for and promotion of patient autonomy and self-determination, the Italian legal system—consistent with European legislation and major international reference documents—provides a series of formal and substantive requirements. Their primary purpose is to ensure that the free determination of the individual concerned, or of persons legally designated to act on their behalf, is formed on the basis of adequate information, provided within what is defined as the informed consent process.

In Italy, regulation of informed consent, as outlined above, is governed by Law No. 219 of 22 December 2017 ("Provisions on informed consent and advance treatment directives"; entry into force: 31 January 2018). As expressly stated in Article 1, Law 219/2017 protects—consistent with Articles 2, 13, and 32 of the Italian Constitution and Articles 1, 2, and 3 of the Charter of Fundamental Rights of the European Union—the right to life, health, dignity, and self-determination of the person, and establishes that no healthcare treatment may be initiated or continued without the free and informed consent of the person concerned, except in cases expressly provided for by law. In line with a now well-established position in legal doctrine and case law, Law 219/2017 also clarifies that informed consent must be understood as a relationship within which (Article 1, paragraph 2) "the patient's decision-making autonomy meets the physician's competence, professional autonomy, and responsibility." The relationship of trust between physician and patient, within which consent is formed, must therefore be regarded as indispensable, as it represents—both formally and substantively—the ethical and legal basis legitimizing the administration of any healthcare treatment.

From a procedural standpoint, the informed consent acquisition process is structured into three fundamental phases, chronologically and logically consecutive: 1) information; 2) discussion and verification of understanding; 3) acquisition of consent or refusal.

The physician therefore has, first and foremost, a duty to inform the patient (and/or the person legally designated to act on their behalf) in an appropriate manner, taking into account: (a) clinically relevant aspects in the specific case; (b) outcomes (including non-clinical outcomes) relevant to the patient; (c) the patient's preferences and values; and (d) aspects related to the context in which the patient lives. With regard to the content of information, and in particular information relating to treatment options, Article 1, paragraph 3, of Law 219/2017 further establishes that "every person has the right [...] to be informed in a complete, up-to-date, and

comprehensible manner about [...] the benefits and risks of indicated diagnostic procedures and healthcare treatments, as well as about possible alternatives and the consequences of refusing healthcare treatment or diagnostic procedures or renouncing them.”⁵ The physician’s task is therefore to present— as personalized as possible—information that is genuinely relevant to the formation of the individual’s free conviction. Law 219/2017 also establishes that (Article 1, paragraph 5) “every person with legal capacity has the right to refuse, in whole or in part, any [...] healthcare treatment indicated by the physician for their condition or individual acts of the treatment itself,” and that (Article 1, paragraph 6) “the physician is required to respect the patient’s expressed wish to refuse or withdraw from healthcare treatment.”

In the case of the technology addressed in this report—the advanced medical device SING IMT, equipped with precision micro-optics and a minimally invasive implantation system—the legal requirements relating to information provision and acquisition of patient consent (or refusal) assume particular significance due to the clinical characteristics of the target population, the invasive nature of the intervention, the complexity of the therapeutic–rehabilitative pathway, and the functional impact that implantation may have on the patient’s daily life.

The SING IMT is integrated into the care pathway of patients with advanced and irreversible AMD (characterized by geographic atrophy or disciform scarring involving the fovea), with severe or profound bilateral visual impairment no longer amenable to conventional therapies. At this stage of the disease, clinical management is therefore primarily situated within low-vision rehabilitation, aimed at helping patients maintain a certain degree of autonomy and quality of life despite visual limitations. Traditional rehabilitative technologies include optical and electronic aids such as magnifying lenses, prismatic glasses, handheld telescopes, closed-circuit television systems, and combined optical systems. Although useful, these tools have significant limitations: they provide a restricted visual field, require complex head or hand movements that may induce vestibular symptoms, and are often poorly suited for patients with motor or cognitive deficits. The SING IMT was therefore developed specifically to overcome these limitations, providing stable image magnification within the eye and enabling functional use of healthy peripheral retinal areas.

It is important to emphasize that although patients aged 55 years and older may be considered eligible for the intervention, in clinical practice the candidate population is characterized by an advanced mean age. This makes comparison with available therapeutic or rehabilitative alternatives particularly relevant from a legal standpoint, as well as careful attention to the quality, completeness, and comprehensibility of the information provided during the informed consent process.

In this context, the physician is required to provide the patient (and/or their legal representative) with clear, complete, up-to-date, and realistic information regarding:

- the characteristics of the device and the purpose of implantation, clarifying that it is not a curative therapy for the disease, but an intervention aimed at improving residual visual function in advanced and irreversible disease;
- the surgical nature of the procedure and its stages;

⁵ With reference to this provision, it should be clarified that providing complete information does not mean that the doctor is required to give all the information relating to the proposed treatment; in fact, an excess of information can be confusing, or even place the patient (and/or their legal representative) in a state of substantial decision-making paralysis.

- the safety profile of the device in light of available data, which remain limited in terms of sample size and long-term follow-up, as well as potential intraoperative issues and postoperative adverse events, whether transient or persistent;
- the functional consequences of implantation, in particular loss of stereoscopic vision and the need to learn a new mode of functional use of both eyes (biocular multiplexing), with the implanted eye used for detail-oriented tasks and the fellow eye for orientation and mobility;
- the demanding and prolonged nature of the postoperative rehabilitation pathway, which may extend from 3 to 6 months and requires high patient adherence;
- the alternatives available in the terminal stage of the disease, consisting essentially of low-vision rehabilitation using traditional aids, highlighting their benefits and limitations;
- the possibility of a discrepancy between objective improvement and subjective tolerability of the new mode of vision, with the risk of persistent blurred vision, diplopia, difficulties with ambulation, or challenges in performing activities of daily living. In a minority but significant proportion of cases, such difficulties may lead to explantation of the device even in the absence of objective clinical complications, with potential repercussions in terms of frustration, stress, loss of trust, and deterioration of quality of life during the adaptation period.

Although information represents the indispensable starting point for enabling the patient (and/or their legal representative) to provide truly free and informed consent, it is essential that the information received be fully understood. In this sense, discussion and verification of understanding—together constituting the second phase of the informed consent process—are crucial. Information must be accompanied by a phase in which the patient can ask questions, express doubts, and clarify expectations regarding realistic benefits of the intervention and the burdens associated with the rehabilitative pathway.

Within this framework, involvement of a caregiver, family member, or trusted person assumes a central role not only in the postoperative and rehabilitative phases, but already in the informed consent process and in joint training on functional use of the device and strategies for adaptation to the new visual condition. Such involvement must, however, take place in accordance with the patient's wishes, who, pursuant to Article 1, paragraph 2, of Law 219/2017, may choose whether or not to avail themselves of the support of a family member or trusted person during the informational and decision-making process. From this perspective, implementation of the SING IMT should, at the organizational level, provide structured information and training pathways directed jointly at the patient and, where desired by the patient, the caregiver, in order to promote truly informed choice and more effective adherence to the rehabilitation program.

In summary, in light of the above considerations, from a legal standpoint it is therefore necessary to ensure that, when implantation of the SING IMT device is proposed, the physician thoroughly reviews the content of the information provided with patients (and/or their legal representatives), responding to any questions in order to enable them to make a truly free and informed decision. This should be done bearing in mind that, as expressly provided by Article 1, paragraph 8, of Law 219/2017, time devoted to communication between physician and patient fully constitutes time of care. In the present case, moreover, involvement of a family member or trusted person in the

informed consent process, as provided for by Article 1, paragraph 2, of Law 219/2017, should be explicitly encouraged by the clinician, while respecting the patient's wishes.

Finally, with regard to aspects related to professional liability, Law 219/2017, by unequivocally establishing that informed consent is the foundation upon which the relationship of care and trust between physician and patient is built, assigns responsibility for proper management of the entire informed consent acquisition process to the physician. In this sense, omissions and/or negligent behavior with respect to informed consent may give rise to professional liability on the part of the physician (regulated, in both criminal and civil terms, by Law No. 24 of 8 March 2017, containing provisions on patient safety and professional liability of healthcare professionals).

10034 – Who can provide consent for [minors and] persons lacking capacity?

At present, the SING IMT is indicated as a therapy for the treatment of patients aged ≥ 55 years with advanced and irreversible AMD; therefore, only adults fall within the target population of this report.

Considering that, upon reaching the age of majority, an individual is presumed to have developed the capacities necessary for self-determination, as described in the previous paragraph, it should generally be considered necessary to obtain the patient's own informed consent for implantation of the medical device. As is well known, however, not all individuals who have reached adulthood are actually able to self-determine and, consequently, to express valid consent to healthcare treatments. In particular—and of relevance here—total or partial impairment of natural capacity, and thus of the capacity for self-determination, may occur precisely in older persons, often as a result of the development and progression of neurodegenerative diseases or conditions.

In the case at hand, the prevalence of AMD increases significantly with age, exceeding 44% among individuals aged 70 to 95 years, and, based on the findings of conducted studies, the target population for implantation of the SING IMT is predominantly composed of individuals older than 65 years. In this context, assessing each individual patient's ability to understand relevant information and to express an informed decision is of central importance, making it necessary, in cases of serious impairment of natural capacity, to refer to the legal protection instruments established by the legal system to ensure protection of the person and the legitimacy of healthcare decisions made in their interest.

In this regard, Article 2 of the Italian Civil Code provides that legal capacity to act—i.e., the ability to perform legal acts aimed at acquiring or exercising one's rights and assuming obligations, which is also necessary in order to provide valid consent in healthcare—is acquired at the age of majority and is retained until death, unless revoked or reduced, respectively, in cases of full guardianship (interdizione) or partial guardianship (inabilitazione). This may occur because legal capacity to act presupposes both legal capacity (conferred on all individuals at birth) and natural capacity, i.e., the ability to understand and to will, which may in certain circumstances be partially or totally impaired. More specifically, full guardianship is provided for by Article 414 of the Civil Code, according to which: "Adults and emancipated minors who are in a condition of habitual mental infirmity that renders them incapable of taking care of their own interests shall be placed under full guardianship when necessary to ensure their adequate protection." Under the

subsequent Article 415 of the Civil Code: “An adult who is mentally infirm, whose condition is not so severe as to require full guardianship, may be placed under partial guardianship. [...]”

With Law No. 6 of 9 January 2004—*Introducing into Book I, Title XII, of the Civil Code Chapter I concerning the institution of “support administration” (amministrazione di sostegno) and amending Articles 388, 414, 417, 418, 424, 426, 427, and 429 of the Civil Code on full and partial guardianship, as well as related implementing, coordinating, and final provisions*—the Italian legislator also introduced the institution of support administration into the legal system. Its purpose is (Article 1, paragraph 1) “to protect, with the least possible limitation of legal capacity, persons who are wholly or partially lacking autonomy in carrying out the functions of daily life, through temporary or permanent support measures.” In other words, the support administrator was introduced to provide further civil-law protection to persons with reduced natural capacity, in particular in carrying out functions of daily life.

With specific reference to the healthcare context, informed consent for healthcare treatments of adult individuals declared totally or partially incapable is regulated by Article 3 of the above-mentioned Law 219/2017⁶, which provides, first, that (Article 3, paragraph 1): “A person [...] lacking capacity has the right to have their abilities of understanding and decision-making enhanced, in compliance with the rights set out in Article 1, paragraph 1⁷. They must receive information about choices relating to their health in a manner suited to their abilities, so as to be placed in a position to express their will.”

Through this provision, the legislator intended to recognize, on the one hand, the fundamental right of patients—even if lacking capacity—to be involved in the consent process regarding healthcare treatments affecting them, and, on the other hand, the need to take into account the actual (residual) abilities of understanding and discernment of each individual patient. This aspect is particularly important in clinical practice, as it requires the physician to carry out a case-by-case assessment to determine whether, to what extent, and how to involve each patient in the decision-making process relating to proposed healthcare treatments.

With particular reference to persons who are totally incapable, Article 3, paragraph 3, of Law 219/2017 further provides that: “Informed consent of a person placed under full guardianship pursuant to Article 414 of the Civil Code is expressed or refused by the guardian, after hearing the person under guardianship where possible, with the aim of protecting the psychophysical health and life of the person in full respect of their dignity.” Therefore, although the wishes expressed by the incapable patient should be taken into account where possible, the person called upon to decide in the interest of the person under full guardianship is, first and foremost, the legal guardian.

Conversely, Article 3, paragraph 4, of Law 219/2017 provides that: “Informed consent of a person placed under partial guardianship is expressed by that person. Where a support administrator has been appointed and the appointment provides for necessary assistance or exclusive representation in the healthcare context, informed consent is expressed or refused also by the support administrator or only by the latter, taking into account the beneficiary’s wishes, in relation to their degree of capacity to understand and to will.”

⁶ Specifically, the law regulates consent to medical treatment for minors and incapacitated persons; the rules established to protect these two categories of individuals are, in fact, frequently presented together, partly because minors strictly speaking represent a specific category of incapacitated persons, as they lack the capacity to act which, as mentioned above, is acquired (except in cases expressly provided for by law) upon reaching the age of majority.

⁷ That is, the ‘right to life, health, dignity and self-determination’.

In accordance with these provisions, and for the purposes of this report, implantation of the SING IMT device in totally incapable patients (under full guardianship) will therefore always require the consent of the patient's legal representative (guardian), as well as, insofar as possible, involvement of the patient themselves in the consent process. With regard to partially incapable patients (under partial guardianship) or individuals for whom a support administrator has been appointed, informed consent must be provided directly by the individuals themselves, or also/exclusively by the support administrator where the appointment provides, respectively, for necessary assistance or exclusive representation in healthcare matters.

In light of the specific characteristics of the clinical-care pathway associated with implantation of the SING IMT device, the above issues take on additional relevance. Access to the technology presupposes active and continuous participation by the patient both in the preoperative phase and in the postoperative phase, the latter characterized by a long and demanding rehabilitation pathway that may extend up to 12 months (with an estimated average duration of about 6 months), requiring a high level of adherence to the rehabilitation program and collaboration with the clinical team.

In this context, patients with even partial impairment of cognitive abilities may face greater difficulty in consistently following the established therapeutic pathway. This makes the role particularly relevant not only of the legal representative called upon to provide informed consent, but also of informal support figures (caregivers), who in practice may not coincide with the formally designated legal representative and who, in fact, are often decisive in ensuring adherence to the rehabilitation pathway and the practical achievability of the expected clinical benefit. In the absence of adequate family or network support, the risk of failure of the therapeutic pathway may be significantly increased.

It follows that these support figures should be appropriately involved, informed, and—where possible—trained from the preoperative phase onwards, in order to promote a realistic understanding of the therapeutic pathway and to sustain patient adherence to the rehabilitation program over time. In parallel, it is important that healthcare personnel be adequately trained to manage a shared preoperative evaluation conducted by a multidisciplinary team, including, in addition to clinical assessment, motivational, cognitive, and social assessment of the patient. From this perspective, staff training should include communication and relational competencies and helping-relationship tools, aimed at realistic and empathetic communication of expectations linked to implantation and the subsequent rehabilitation pathway, as well as support for compliance and continuity of care.

These elements are also relevant from the perspective of equitable access to the technology. The requirement for high compliance may in fact translate, in clinical practice, into a de facto selection criterion for candidates for implantation, with the potential risk of excluding individuals who, although clinically eligible, experience greater difficulty sustaining the therapeutic pathway due to impaired cognitive capacities. Such exclusion, if not adequately grounded in individualized and proportionate clinical assessments, could be in tension with the principle protecting the right to health under Article 32 of the Italian Constitution, as well as the principle of non-discrimination in access to care, as derived from Article 21 of the Charter of Fundamental Rights of the European Union and, more generally, from the principles of equity and universality underpinning the National Health Service.

This is particularly relevant with regard to the subgroup of elderly patients who present impaired decision-making capacities, who are in a condition of double vulnerability—linked both to advanced age and reduced self-determination—and who therefore risk further marginalization in access to highly complex healthcare technologies.

It follows, from the perspective of correct implementation of the technology and respect for the principles of substantive equality and protection of the person, that clinical eligibility criteria should be complemented by a formalized assessment of the patient's support context and the availability of adequate care resources—not as a basis for automatic exclusion from access to the technology, but rather as a foundation for adopting organizational and support measures suitable to make the exercise of the right to health effective also for the most fragile patients.

Ethical Aspects

F0014 – Does implementation or use of the technology affect the realization of fundamental human rights?

Protection of human rights represents one of the primary purposes for which legal systems, both national and supranational, are established, and it justifies the introduction of rules governing human activities in both their individual and collective dimensions.

Human rights are fundamental and inalienable rights, meaning rights that must always be recognized for every individual, regardless of origin, characteristics, ideas, preferences, affiliations, or the places in which a person is born, grows up, and lives. These rights are recognized in numerous international instruments (including, by way of example: the Universal Declaration of Human Rights [3], the European Convention for the Protection of Human Rights and Fundamental Freedoms [4], and the Charter of Fundamental Rights of the European Union [5]), which are recognized and applied in Italy both directly and through specific legislation enacted to integrate their principles into the national legal system.

In addition to international law (both treaty-based and customary), which protects, among others, the right to life, personal liberty, and self-determination, the Italian State grants constitutional relevance to the protection of human rights, starting with Article 2 of the Constitution, pursuant to which “The Republic recognizes and guarantees the inviolable rights of the person, both as an individual and within the social groups in which their personality is expressed, and requires the fulfillment of the mandatory duties of political, economic, and social solidarity,” and Article 13, which provides that “Personal liberty is inviolable. No form of detention, inspection, or personal search, nor any other restriction of personal liberty, is permitted except by reasoned act of the judicial authority and only in the cases and manner provided by law [...]”.

As anticipated, constitutional relevance is also explicitly granted to the right to health, understood in the broad sense defined by the World Health Organization as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” [6]. Article 32, paragraph 1, of the Constitution indeed provides that: “The Republic safeguards health as a fundamental right of the individual and as an interest of the community, and guarantees free care to the indigent.”

In implementation of the constitutional mandate, the task of the National Health Service (NHS) is therefore to guarantee all citizens, under conditions of equality, universal access to equitable provision of healthcare services. The fundamental principles upon which the NHS has been based since its establishment by Law No. 833 of 23 December 1978 are universality, equality, and equity, alongside other organizational principles essential for healthcare planning. Among these, the principle of person-centeredness is particularly relevant and can be expressed through a series of rights exercisable by individual citizens, such as freedom to choose the place of care, the right to be informed about one's illness and available therapeutic alternatives, the right to give or withhold consent, the right to privacy, and the corresponding duties of healthcare professionals [7].

The need to ensure respect for human rights is also explicitly recalled in the aforementioned Law 219/2017, which, in Article 1, protects—consistent with the principles set out in Articles 2, 13, and 32 of the Italian Constitution and Articles 1, 2, and 3 of the Charter of Fundamental Rights of the European Union—the right to life, health, dignity, and self-determination of the person, and establishes that no healthcare treatment may be initiated or continued without the free and informed consent of the person concerned, except in cases expressly provided for by law.

As already emphasized (including in other domains of this report⁸), at the global level AMD represents one of the leading causes of visual disability. In 2015, it was the third most common cause of moderate-to-severe visual impairment, with a prevalence of 8.7% among individuals aged 45 to 85 years and 0.4% for the advanced form; in industrialized countries, it represents the leading cause of irreversible vision loss in individuals over 65 years of age and accounts for approximately 9% of all cases of blindness. In this context, implementation of the SING IMT medical device, having the potential to improve health conditions and quality of life of patients with end-stage AMD, may concretely contribute to the effective realization of the universally recognized and constitutionally protected right to health in a population whose needs remain largely unmet due to the limited effectiveness of traditionally used therapies.

With regard to the impact of technology implementation on realization of fundamental human rights, the issue of equitable access to the technology for individuals in conditions of particular vulnerability—such as elderly patients with impaired decision-making capacity—is also relevant. The characteristics of the clinical-care pathway associated with implantation, which require a high level of active participation and compliance over the medium to long term, may in practice lead to a de facto selection of candidates, with the risk of excluding individuals who, although clinically eligible, experience greater difficulty sustaining the therapeutic pathway.

Such dynamics, if not adequately governed through organizational and support measures, could come into tension with the principles of substantive equality and non-discrimination, as well as with the right to health, protected by Articles 3 and 32 of the Italian Constitution and Article 21 of the Charter of Fundamental Rights of the European Union, in addition to the principle of equity underpinning the NHS. It follows that implementation of the SING IMT should be accompanied by measures designed to ensure genuinely equitable access to the technology also for the most fragile individuals, avoiding situations in which extra-clinical factors translate into indirect barriers to the exercise of fundamental human rights.

⁸ See, in particular, domain CUR.

Authorization and Safety

10015 – What authorizations and registrations does the technology hold?

In general, placing medical devices on the market, making them available, and putting them into service within Italian territory is currently permitted only for devices bearing the CE marking⁹, which certifies their conformity with the requirements established by Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009, and repealing Council Directives 90/385/EEC and 93/42/EEC.

Before entry into force of Regulation (EU) 2017/745, medical devices were regulated by Directive 93/42/EEC, transposed in Italy by Legislative Decree 46/97. In order to adapt national legislation to the new EU provisions, Regulation (EU) 2017/745 was followed by Legislative Decree No. 137 of 5 August 2022, published in the Official Gazette on 13 September 2022 and entered into force on 28 September 2022, which currently governs aspects of exclusively national competence, in continuity with the previous Legislative Decree 46/97 [8].

The SING IMT medical device—commercial name of the Tsert SI™ system, model NG SI IMT 3X, an implantable device (Implantable Miniature Telescope) NG SI IMT 3X, packaged together with the Tsert SI insertion system—is manufactured by Samsara Vision, Inc., a private medical device company specializing in the research, development, production, and commercialization of implantable ophthalmic devices.

This device represents the evolution of the IMT system (already approved in 2010) and obtained CE marking for the European Union in 2020, with certification issued by Notified Body 0483 (MDC, Medical Device Certification GmbH) in accordance with Directive 93/42/EEC on medical devices¹⁰. The indication for which CE marking was obtained for the SING IMT concerns treatment of patients with bilateral central scotomas due to end-stage AMD, with stable moderate to profound visual impairment.

In particular, the SING IMT is placed on the market as a legacy device pursuant to Article 120.3 of Regulation (EU) 2017/745, under which: “By way of derogation from Article 5 of this Regulation, a device with a certificate issued in accordance with Directive [...] 93/42/EEC [...] may be placed on the market or put into service provided that from the date of application of this Regulation it continues to comply with one of those Directives and provided that there are no significant changes in the design and intended purpose. However, the requirements of this Regulation relating to post-market surveillance, market surveillance, vigilance, registration of economic operators and devices shall apply and shall replace the corresponding requirements in those Directives.” In other words, although placed on the market in partial derogation from the provisions of Regulation (EU) 2017/745, the SING IMT is subject to all requirements imposed by that Regulation with regard to post-market surveillance, market surveillance, vigilance, registration of economic operators and devices, and certification notifications, which replace the corresponding requirements of the Directives.

⁹ More specifically, medical devices may only be placed on the market by the manufacturer if they have a valid CE certificate, unlike making them available, i.e. supplying them for distribution, consumption or use, which may be done by the distributor even after the expiry date of the certificate, provided that the certificate was valid at the time of placing on the market (see Art. 2, Definitions 27), 28) and 29), EU Regulation 2017/745).

¹⁰ Currently, the device is not approved by the FDA in the United States, where it is still undergoing trials.

10017 – What do binding laws/regulations require with regard to the safety of the technology, and how should this aspect be addressed when implementing the technology?

As already emphasized, within the European Union Regulation (EU) 2017/745 has reshaped the regulatory framework governing medical devices, with the aim of ensuring a robust and sustainable system, as well as transparent procedures capable of fostering innovation while simultaneously guaranteeing a high level of safety. In particular, in order to ensure protection and safeguarding of the health and safety of patients, users, and all parties who in various ways interact with medical devices, the Regulation provides for a significant strengthening of the rules governing vigilance and post-market surveillance. These mechanisms ensure continuous monitoring of incidents occurring with devices after they are placed on the market, also through collaboration among all stakeholders involved in the system.

In Italy, among these stakeholders, the Ministry of Health monitors the activities of medical device manufacturers/authorized representatives and healthcare professionals, collecting and analyzing all data flowing into the vigilance system. The Ministry of Health also performs a detailed assessment of reported serious incidents and, where appropriate, disseminates information in order to reduce the likelihood of recurrence of the same type of incident.

The medical device sector is currently undergoing a transitional phase in which certain provisions of Regulation (EU) 2017/745, although binding from the date of application of the Regulation, cannot yet be fully implemented in the manner prescribed until the European database on medical devices (EUDAMED) [9] becomes fully functional (as provided for in Article 123(3)(d) of the Regulation). In this regard, on 27 November 2025 the European Commission announced, through Implementing Decision (EU) 2025/2371, the full functionality of four of the six EUDAMED modules, as published in the Official Journal of the European Union. This decision triggered a six-month transitional period, at the end of which (28 May 2026) use of the first four EUDAMED modules will become mandatory.

As anticipated in the previous paragraph, although EU legislation is directly applicable within the Italian legal system, it required adaptation of national legislation—particularly with respect to organizational aspects of national competence—which was implemented through Legislative Decree No. 137/2022. In particular, Article 10 of that Decree, by referring to specific ministerial decrees for regulation of the timing and modalities of incident reporting, sets out the obligations for manufacturers and healthcare professionals in cases of serious incidents, non-serious incidents, and complaints involving devices after they are placed on the market.

Pending adoption of these ministerial decrees, Circular of 29 November 2022 (Protocol No. 87235) was issued, providing operational guidance on the modalities and timelines for reporting serious incidents, non-serious incidents, complaints, field safety corrective actions, as well as periodic summary reports and trend reports. These operational guidelines are addressed both to economic operators (manufacturers, authorized representatives, importers, distributors) and to users (healthcare professionals, patients, and lay users).

One of the main innovations introduced by Regulation (EU) 2017/745 is the definition of a serious incident. The distinction between a serious incident and a non-serious incident essentially lies in

the actual or potential consequences arising from the incident involving a device on the market. According to Article 2 of the Regulation:

- “incident” means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side effect;
- “serious incident” means any incident that directly or indirectly has led, might have led, or might lead to one of the following:
 - a) death of a patient, user, or other person;
 - b) serious deterioration in the state of health, temporary or permanent, of a patient, user, or other person;
 - c) a serious public health threat.

Within the vigilance system, healthcare professionals play a key role in communicating incidents related to use of a medical device, as they are generally the first to ascertain their occurrence. Consequently, current regulations require public and private healthcare professionals, based on what they observe in the course of their professional activities, to promptly notify (within no more than 10 days) the Ministry of Health of any serious incident, even if only suspected, related to use of a medical device. Healthcare professionals may also report non-serious incidents to the Ministry of Health.

Healthcare professionals are always required to notify serious and non-serious incidents to the manufacturer/authorized representative of the device involved, thereby enabling the latter to initiate an investigation aimed at determining the causes.

Article 87 of Regulation (EU) 2017/745 further defines manufacturers' obligations, modalities, and timelines for reporting serious incidents to the Competent Authority. In particular, the manufacturer, as the economic operator legally responsible for devices placed on the market under its name, must report serious incidents involving its device to the Ministry of Health and, where a potential risk associated with use of its devices is identified, must voluntarily undertake field safety corrective actions proportionate to the severity of the risk. These actions may result in dissemination of new safety information or withdrawal of the device from the market. Finally, when becoming aware of a serious incident, the manufacturer must, without delay, conduct all necessary investigations relating to the device involved, carry out a careful risk assessment, and, where appropriate, implement corrective actions to reduce that risk.

The Ministry of Health is responsible for monitoring investigations carried out by the manufacturer or its authorized representative, in order to assess the corrective actions implemented and to monitor their effectiveness. If necessary, the Ministry of Health, as the Competent Authority, may at any time intervene autonomously by conducting its own investigations and imposing corrective measures deemed necessary, always with a view to promoting and safeguarding public health and safety. Where it considers that there are risks to public health, the Ministry of Health may also impose restrictions and/or limitations on the marketing or putting into service of medical devices.

An important operational tool within the vigilance system is the national medical device vigilance network, established by Ministerial Decree of 31 March 2022, which was created to promote timely

exchange of information among the Ministry of Health, the Regions and Autonomous Provinces, and healthcare organizations with regard to serious incidents, non-serious incidents, and safety actions¹¹.

Clearly, the vigilance and post-market surveillance system outlined by Regulation (EU) 2017/745 applies to all medical devices, but with modalities and levels of intensity differentiated (also) according to the risk profile. In this regard, decisive importance is attached to the classification of medical devices set out in Article 51 of the Regulation, into classes I, IIa, IIb, and III, described in detail in Annex VIII to the Regulation.

For the purposes of this report, classification of the SING IMT as a Class IIb implantable medical device entails significant regulatory consequences, given the medium–high risk level associated with this category and its intended long-term implantation in the human body. Compared with Class IIa devices, which present a lower risk profile and are generally intended for short-term intracorporeal use, Class IIb devices are subject to a more stringent control regime throughout the entire product life cycle, from pre-market evaluation through post-market surveillance.

In particular, with regard to post-market surveillance, classification of the SING IMT as a Class IIb device entails application of stricter obligations for continuous monitoring of performance and safety in real-world clinical practice, reporting of incidents and field safety corrective actions, and periodic updating of the clinical evaluation. These obligations are also reflected at the level of user centers and healthcare professionals, who are required to actively participate in vigilance systems and in the collection of long-term follow-up data on implanted patients.

With specific reference to the SING IMT medical device, considering that safety requirements concern the entire pre- and postoperative pathway in which the patient is involved, it is therefore necessary to:

- carefully select patients according to clinical and functional criteria, in order to reduce the risk of adverse events;
- provide complete, clear, and understandable information on possible postoperative risks and on the rehabilitation pathway, so that the patient can participate consciously in the care process;
- implement structured postoperative clinical monitoring protocols to promptly identify and manage any complications or functional adaptation issues;
- document all management and surveillance phases, in order to ensure traceability and professional accountability in the event of adverse events;
- train clinical staff and, where necessary, caregivers, so that they are prepared to support the patient throughout the entire therapeutic and rehabilitative pathway.

In summary, binding regulations require that safety be addressed in a systematic, multidisciplinary, and well-documented manner, taking into account both objective clinical risks and the functional and psychosocial aspects related to use of the device.

¹¹ The information system supporting the network, called Dispovigilance, has been fully operational since 13 October 2022.

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