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Final Degree Project

USE OF IN-HOUSE THREE-DIMENSIONAL PRINTED ANATOMICAL MODELS IN PRE-OPERATIVE PLANNING TO IMPROVE SURGICAL OUTCOMES IN PATIENTS UNDERGOING SURGERY FOR ISOLATED ORBITAL FLOOR FRACTURES

An open-label, randomized, clinical trial

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1. ABSTRACT

BACKGROUND: Orbital floor fractures are frequent among young adults, and their anatomy poses a challenge for any surgeon. Accurate reconstruction is imperative to restore normal anatomy and prevent potential sequelae such as persistent enophthalmos, which may lead to visual implications, including diplopia. An innovative approach to improve accurate reconstruction is based on the integration of in-house three-dimensional (3D) printing into pre-operative planning. This methodology involves the creation of individualized anatomical models based on patients' pre-operative CT scans, offering precise representations of unique fracture characteristics.

OBJECTIVES: The main objective is to investigate the impact of using in-house 3D printed anatomical model for pre-operative planning in isolated orbital floor fractures on the occurrence of persistent enophthalmos, measured 1 month after surgery. Secondary objectives include assessing post-operative complications 1 month after surgery (persistent diplopia, infraorbital nerve dysfunction and restricted EOM motility) and evaluating patients' understanding and satisfaction regarding the information received before the surgical procedure.

DESIGN: This study is designed as a multicentric, prospective, open-label, randomized clinical trial carried out from November 2023 to March 2027.

PARTICIPANTS AND METHODS: A total of 132 patients undergoing surgery for an isolated orbital floor fracture will be enrolled using a non-probabilistic consecutive sampling method. They will be randomly assigned to Group A (pre-operative planning using in-house 3D printed models) or Group B (conventional pre-operative planning). Data on study variables will be collected and analysed. By investigating the effectiveness of incorporating 3D printed anatomical models in pre-operative planning, this study seeks to contribute to the advancement of Oral and Maxillofacial (OMF) surgical practices, with potential implications for reducing complications and improving both functional and aesthetic outcomes.

KEYWORDS: Orbital floor fractures, Enophthalmos, Post-operative complications, Persistent diplopia, Infraorbital dysfunction, Restricted extraocular muscles motility, Hertel exophthalmometer, Visual Analogue Scale, Understanding and Satisfaction

2. ABBREVIATIONS

- **3D**: Three-dimensional
- **3DP PoC**: 3D Printing Point-of-Care
- **AM**: Additive manufacturing
- **BAOMS**: British Association of Oral and Maxillofacial Surgeons
- **CAS**: Computer-assisted surgery
- **CC**: Clinical Coordinator
- **CEIC**: Comitè Ètic d'Investigació Clínica
- **CI**: Co-Investigator
- **CT scan**: Computed Tomography scan
- **DICOM**: Digital Imaging and Communications in Medicine
- **DM**: Data Manager
- **EACMFS**: European Association for Cranio-Maxillo-Facial Surgery
- **EOM**: Extraocular muscles
- **HUAV**: Hospital Universitari Arnau de Vilanova de Lleida
- **HUB**: Hospital Universitari de Bellvitge
- **HUGTP**: Hospital Universitari Germans Trias i Pujol
- **HUJ23**: Hospital Universitari Joan XXIII de Tarragona
- **HUJT**: Hospital Universitari Doctor Josep Trueta
- **HUVH**: Hospital Universitari Vall d'Hebron
- **ICS**: Institut Català de la Salut
- **IO**: Intraocular
- **IP**: Independent physician
- **IS**: Independent statistician
- **MI**: Main Investigator
- **MVAs**: Motor vehicle accidents
- **OCR**: Oculocardiac reflex
- **OMF**: Oral and Maxillofacial
- **PLA**: Polylactic acid
- **PSIs**: Pacient-specific implants
- **REDCap**: Research Electronic Data Capture

- **SCBCMO**: Societat Catalano-Balear de Cirurgia Maxil·lofacial i Oral
- **SECOM CyC**: Sociedad Española de Cirugía Oral y Maxilofacial y de Cabeza y Cuello
- **SLA**: Stereolithography
- **SPSS**: Statistical Package for Social Sciences
- **STL**: Standard Triangulation Language
- **TJR**: Total Joint Replacement
- **VAS**: Visual Analogue Scale
- **VSP**: Virtual surgical planning
- **WHO**: World Health Organization

3. INTRODUCTION

3.1. Orbital anatomy

3.1.1. Osteology of the orbit

The orbits are bilateral bony cavities that house the globes. The orbital cavity is a conical structure with a quadrilateral base anteriorly, forming the orbital aperture, and the apex posteriorly, which terminates at the optic foramen. In general, the bone is thickest at the apex, thins as the walls diverge anteriorly, and then thickens again at the rims on the surface of the face. The thickened rim can resist fracture forces more effectively than the weaker walls (medial wall and floor), as shown on *Figure 1*. The floor of the orbit is most susceptible to fracture when there is direct force on the ocular globe as it is thin and unsupported, because of the presence of the maxillary sinus below (1–3).

The orbits are formed by seven bones and defined by walls, as seen on *Figure 2* (1,3–5):

- **Lateral wall**: Composed of the greater wing of the sphenoid and the frontal and zygomatic bones. It is the thickest wall and the least projected rim, facilitating lateral vision.
- **Orbital floor**: Formed by the sphenoid, the orbital process of the palatine bone, and the orbital process of the maxillary bone. It exhibits a gradual slope from the medial to lateral side and a “lazy S” shape in the sagittal view, with the anterior part concave and the posterior convex. This anatomical subtlety is crucial during the repair of orbital floor fractures. Accurately re-creating this gentle curvature is essential for restoring normal anatomy and preventing enophthalmos. The infraorbital nerve, a branch of V2 (maxillary branch of the trigeminal), closely follows the orbital floor, providing sensory innervation to the lower eyelid, midface, upper lip, and gums. In orbital floor fractures or repair procedures, this nerve is at risk of injury potentially resulting in paresthesia.
- **Medial wall**: Constituted by the lesser wing of the sphenoid, the ethmoid bone, the lacrimal bone and the frontal process of the maxilla. This wall separates the ethmoid sinuses and nose from the orbit.

- **Orbital roof**: Formed by the sphenoid and frontal bone, which delineates the orbital contents from the cranial cavity. Its triangular shape culminates in the optic foramen, which is the entry of the optic nerve into the orbit. The roof is separated from the lateral wall by the superior orbital fissure, which is a passage of entry for the cranial nerves III (oculomotor), IV (trochlear), V1 (ophthalmic branch of the trigeminal) and VI (abducens), as well as the ophthalmic vein.

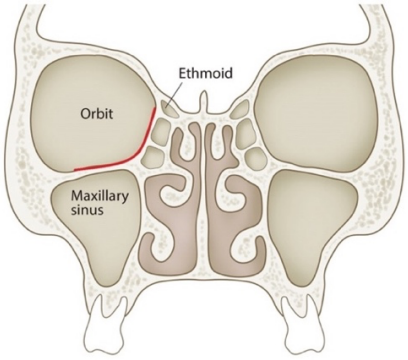


Figure 1. Common fracture sites, medial wall and orbital floor (red line). Extracted from: (2)

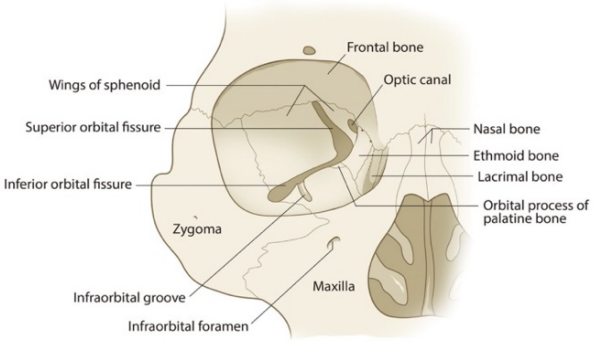


Figure 2. Bones and fissures of the orbital cavity. Extracted from: (2)

3.1.2. Muscles of the orbit, innervation and their function

Muscles in relation to the orbit can be divided into the muscles associated with the lids and the extraocular muscles (EOM) associated with the globe (1,3,6).

The muscles of the lid are:

- **Orbicularis oculi**: This muscle has a palpebral and an orbital portion and lies just beneath the skin, as seen on *Figure 3*. Its palpebral component is present in the superior and inferior eyelids. The contraction of the orbicularis oculi controls the closure of the upper eyelid, and it receives innervation from the facial nerve.

- **Levator palpebrae superioris**: It is the elevator of the upper eyelid, and it receives innervation from the III cranial nerve (oculomotor).

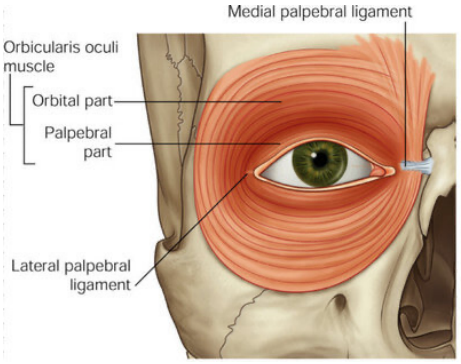


Figure 3. Orbicularis oculi muscle. Extracted from: (7)

The EOM, responsible for eye movement, originate at the annulus of Zinn and travel anteriorly to insert into the globe. The exception is the inferior oblique, which originates on the maxillary bone. The EOM and their functions are:

- **Superior rectus**: It inserts into the upper part of the sclera, facilitating eye elevation. Innervated by the oculomotor nerve.
- **Medial rectus**: It inserts into the medial surface of the sclera, helping in medial eye movement (adduction). Bilateral action of the muscles produces medial convergence of both corneas. Innervated by the oculomotor nerve.
- **Lateral rectus**: It inserts into the lateral surface of the sclera. Its primary function is to facilitate lateral eye movement (abduction). Innervated by the abducens nerve.
- **Inferior rectus**: It inserts into sclera below the cornea. It is responsible for eye depression and lateral rotation. The inferior rectus, as well as the medial rectus, can be implicated in entrapment due to orbital trauma. Innervated by the oculomotor nerve.
- **Superior oblique**: It is attached via a trochlea to the orbit on the medial side of the roof. It rotates the globe inferiorly (intorsion). Innervated by the trochlear nerve.
- **Inferior oblique**: It produces corneal elevation and helps in external eye movement (extorsion). Innervated by the oculomotor nerve.

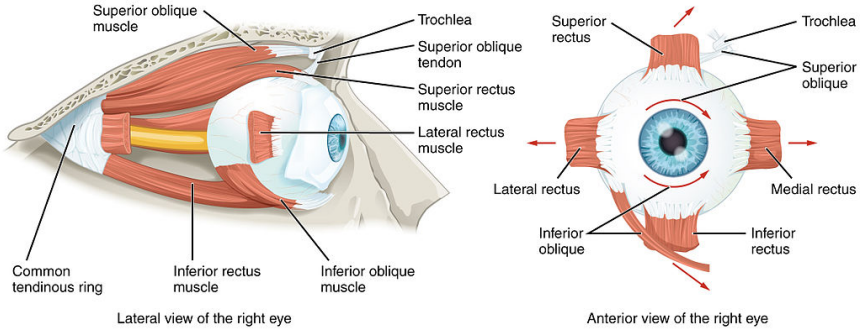


Figure 4. EOM and their movement. Extracted from: (8)

Therefore, the EOM are responsible for the primary positions of gaze. Six cardinal positions are identified, with each eye muscle primarily responsible for moving the eye towards these positions. Additionally, there are the nine **diagnostic gaze positions** in which deviations are measured. As shown on *Figure 5*, these include the six cardinal positions, primary position, elevation, and depression (9).

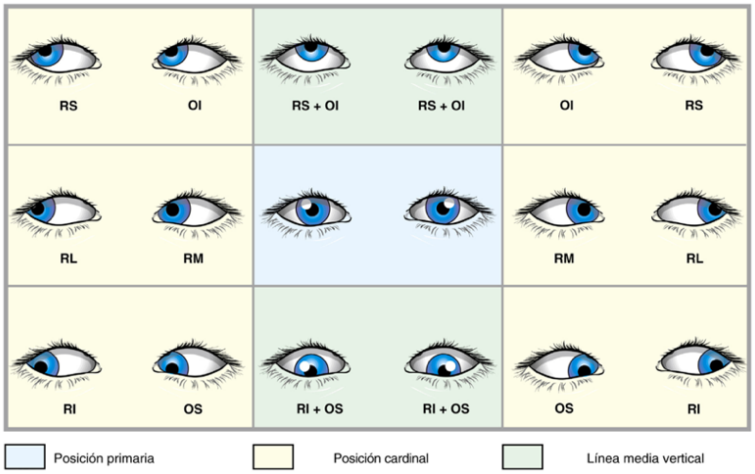


Figure 5. Diagnostic gaze positions. OI = Inferior oblique; OS = Superior oblique; RI = Inferior rectus; RL = Lateral rectus; RM = Medial rectus; RS = Superior rectus. Extracted from (9)

3.2. Orbital fractures

Orbital fractures are unique among cranio-maxillofacial fractures due to their functional, cosmetic and psychological implications. Managing orbital fractures poses a challenge to every surgeon, given the complex anatomy, relationship to vital structures such as the eye globe and the brain, and its direct influence on one of the most precious of senses, vision (1).

Studies have estimated that orbital fractures constitute approximately **10 to 25% of all facial fractures** (10,11). The most common etiologies of orbital fractures, similar to all facial fractures, are **assaults** and **motor vehicle accidents (MVAs)**, followed by falls and trauma related to sports activities (12). These fractures are more frequent in **males** than females and typically occur during the teenage and **young adult years** (13).

3.2.1. Biomechanics of injury and blowout fractures

Blowout fractures were first described in 1957 by Smith and Converse as a fracture of the orbital floor caused by a sudden increase in intra-orbital pressure (14). These fractures involve entrapment or herniation of periorbital tissues, resulting in restricted EOM motility and/or enophthalmos due to reduction in the volume of intraorbital contents (1). Blowout fractures are also described as isolated fractures of the orbital walls without involvement of the orbital rim (15).

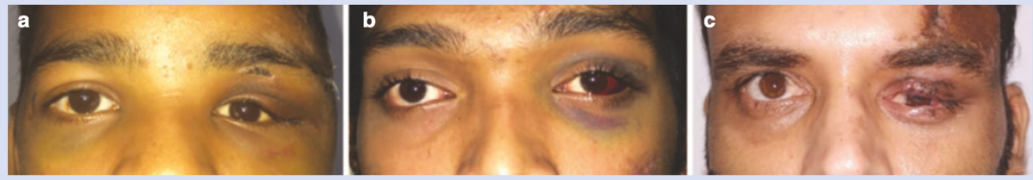
Although most studies agree that both mechanisms are implicated, two different theories have been proposed as the trauma mechanism of orbital wall fractures (1,5,15,16):

- **Hydraulic mechanism**: Described in 1943 by Pfeiffer, also called globe-to-wall theory. This theory suggests that blunt trauma to the eye increases the intraorbital pressure, which then causes a fracture of the weakest area of bone, often blowing out the orbital floor.
- **Buckling mechanism**: This theory suggests that the orbital walls bend in response to direct impacts towards the orbital rim, causing a fracture at its weakest points.

3.2.2. Initial evaluation of orbital fractures

Patients with a history of trauma to the periorbital area should undergo evaluation for potential orbital fractures. Assuming hemodynamic stability, a thorough anamnesis and a targeted ophthalmologic examination must be conducted to assess for both intraocular (IO) and extraocular injuries (4). The ophthalmic examination should include the assessment of visual acuity, visual fields, pupils, EOM motility and alignment, IO pressure, periorbital area, globe position, and integrate a fundoscopic examination. After the ophthalmologic evaluation, it is essential to examine the skeletal and soft tissue components of the orbit. *Table 1* illustrates the common clinical traits observed in patients with orbital trauma.

Table 1. Common clinical characteristics in orbital trauma. Images demonstrating (a) edema of the left periorbital area, (b) left-sided periorbital ecchymosis and subconjunctival haemorrhage, and (c) soft tissue injury involving the left eyelid. Extracted from (1)

CLINICAL CHARACTERISTICS	
▪ Periorbital edema ▪ Periorbital ecchymosis ▪ Contusions and hematomas ▪ Subcutaneous emphysema with crepitus	▪ Lacerations involving the eyelids ▪ Subconjunctival haemorrhage ▪ Injuries to the canthal apparatus[1] ▪ Neurological deficits of the infraorbital and facial nerves
	

Furthermore, there are some other important clinical signs and symptoms to consider in orbital trauma:

- **Retrobulbar haemorrhage**: It occurs due to the accumulation of blood in the retrobulbar space, leading to increased intraorbital pressure. This elevated pressure results in the compression of the optic nerve and reduction of perfusion to the eye. Clinically, retrobulbar haemorrhage presents as reduced EOM

[1] Meeting point of the upper and lower eyelid.

motility, elevated IO pressure, proptosis, and diminishing vision (1). Due to the risk of permanently losing vision, urgent intervention is required (4).

- **Oculocardiac reflex (OCR)**: Defined by a decrease in heart rate by more than 20% following globe pressure or traction to the EOM, resulting in sinus bradycardia. This reflex may be accompanied by symptoms such as nausea, vomiting and dizziness (17). The most common etiology is the incarceration of the inferior rectus muscle in orbital floor fractures (18).

- **Hypophthalmos**: Also known as hypoglobus, is defined as the downward displacement of the eye globe due to a disruption in the anatomical integrity of the orbital floor. Hypophthalmos manifests as a change in the horizontal pupillary levels (1).

Once the clinical examination has been completed, an imaging test is necessary. The **CT scan** is considered the "gold standard" in orbital trauma. These scans are typically ordered with fine cuts of 0.5 mm and taken in all three planes. Coronal and sagittal projections are important in diagnosing floor and roof fractures, while axial scans offer more detailed information about medial and lateral wall fractures (1).

3.2.3. Orbital floor fractures

The fractures involving the **orbital floor** are the most common fractures of the internal orbit, either in isolation or concomitant to other facial fractures. The internal orbit includes the roof, the floor, and the medial and lateral walls (1).

3.2.3.1. Management of orbital floor fractures

Many orbital floor fractures do not result in long-term functional or cosmetic defects and, therefore, do not require surgical intervention (19). However, predicting future outcomes in the acute setting with soft tissue edema can be challenging.

Indications for surgical intervention in orbital floor fractures can be classified as absolute and relative (1,4,16):

- **Absolute indications**:
  - Acute injury to the orbit with enophthalmos of 2 mm or more and/or hypophthalmos
  - Severe restriction of ocular motility with CT-evidenced muscle entrapment or incarceration of periorbital soft tissue
  - "White eye blowout"[2] fracture in a child or young adult with severe restriction of ocular motility and OCR
- **Relative indications**:
  - Defects of the orbital floor larger than 50% of the orbital floor area or greater tant 20 x 20 mm in size, especially in the zone between the floor and the medial wall
  - Diplopia that is non-resolving and persistent for more than 2 weeks due to entrapment or fibrosis of orbital soft tissue

Surgical treatment is **relatively contraindicated** if the orbital floor fracture is associated with ophthalmic injuries (e.g. retinal tears, hyphema, displacement of the lens, ruptured globe or avulsion injuries of the globe). Additionally, it is contraindicated if the patient has vision loss in one eye, and the only seeing eye is involved in the fracture (1).

The **timing for intervention** can be divided into three categories:

Table 2. Chart showing timing for orbital floor reconstruction surgery. Extracted from (1)

IMMEDIATE (<24 hours)	- "White eye blowout" fracture or vision threatening emergency - CT evidenced EOM entrapment and OCR
EARLY (<14 days)	- CT evidenced EOM entrapment and non-resolving diplopia - Early onset enophthalmos/hypopthalmos - >50% or >2x2 mm orbital floor defect
LATE (>14 days)	- Non-resolving symptoms - Late enophthalmos/hypophthalmos

[2] "White eye blowout" fracture is a single or multiple wall orbital fracture with intact orbital rim, herniation and entrapment of periorbital soft tissues, restrictive strabismus and a clinically "quiet eye".

The **surgical approaches** to orbital floor fractures depend on the injury site, surgeon preference, and equipment availability. Approaches to the orbital floor can be classified as **transcutaneous** or **transconjunctival**, with the last-mentioned considered the standard and most used approach. Transcutaneous incisions are rarely used due to inferior cosmetic results and potential development of ectropion (lower eyelid turns outwards) due to scarring of the orbital septum (4). The advantages of the **transconjunctival approach** include excellent cosmetic outcome, minimal incidence of ectropion, and extensive access up to 270º to the floor, medial and lateral walls (1).

In *Figure 7*, the surgical management of an orbital floor fracture can be seen, illustrated with images from a surgery.

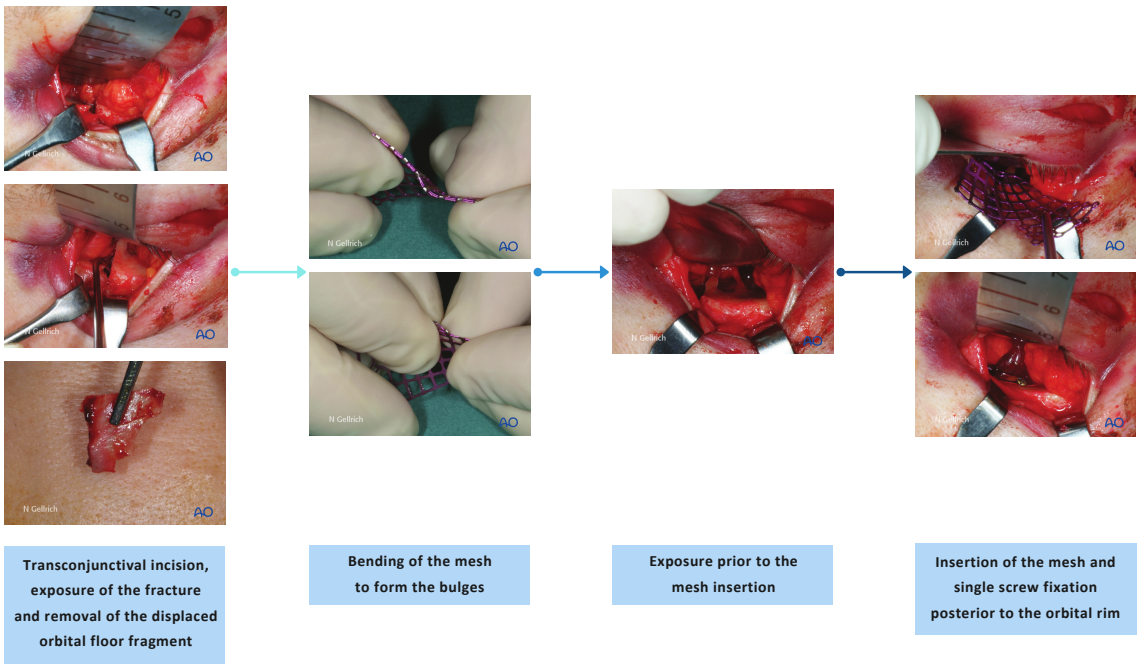


Figure 6. Diagram illustrating the process of orbital floor fracture reconstruction. Images extracted from (20)

Various **materials** are suitable for **orbital implants**, ranging from autogenous grafts such as bone or cartilage, to alloplastic implants. Among these options, **titanium** is the most used material. It has the advantage of being thin, malleable, and widely available, while providing excellent support. Titanium also displays excellent osteointegration, making it a highly suitable metal for repairing bony defects (16).

3.2.3.2. Post-operative care and complications

During **post-operative care**, it is important to watch out for acute complications such as infection and visual symptoms. Visual acuity and pupillary function must be monitored closely as soon as the patient wakes up from anesthesia and then at regular intervals until discharge. Keeping the patient's head in an upright position may significantly improve periorbital edema and pain. To prevent orbital emphysema, nose-blowing should be avoided for at least 10 days following the orbital fracture repair (20,21).

Complications related to the management of orbital floor fractures can be categorized into immediate and delayed complications, with the most common ones outlined in *Table 3*. Additionally, less frequent complications may include intraoperative hemorrhage, ectropion, hypertrophic scar formation, and, in rare cases, blindness (1).

Table 3. The most common immediate and delayed complications associated with the management of orbital fractures. Extracted from (1)

IMMEDIATE COMPLICATIONS	DELAYED COMPLICATIONS
- Edema - Infection and/or wound dehiscence - Implant malposition - Extrusion of the implant	- Persistent enophthalmos - Persistent diplopia with altered vision - Restricted EOM motility due to fibrosis and adhesion - Infraorbital nerve dysfunction

3.2.4. Enophthalmos

Enophthalmos is defined as a **retrodisplacement** of the eye globe within the bony confines of the eye socket (22). It is estimated that approximately 30% of patients undergoing surgical treatment for orbital floor fractures will suffer from persistent enophthalmos, which can have both aesthetic (eye position asymmetry) and visual repercussions. Visual implications result from differences in globe position between the two eyes, leading to diplopia (23).

Clinically, enophthalmos is detectable through an exaggerated suprapalpebral fold and reduced projection when viewed from below (1). Enophthalmos can be measured using a **Hertel exophthalmometer**, which is a handheld instrument with two identical measuring devices (one for each eye), connected by a horizontal bar. When aligned correctly, the set of mirrors reflect a lateral image of each eye along with a measurement scale calibrated in millimetres (24). It measures the distance between temporal orbital rims, the deepest palpable point of the angle, and the apex of the cornea. Enophthalmos is diagnosed when the difference between both eyes is **more than 2 mm**.

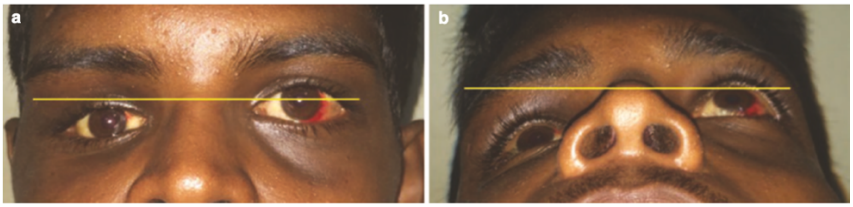


Figure 7. Clinical photograph of a patient with both (a) hypophthalmos and (b) enophthalmos of the right eye globe. Extracted from (1)

3.2.5. Recent advances in management of orbital fractures

In the last years, the availability of 3D printing has revolutionized patient care, providing improved tools and prototypes for surgical solutions. Orbital reconstruction stands as one of the most challenging areas in the management of craniofacial trauma, always incorporating cutting-edge technology to enhance outcomes.

Significant advances in orbital reconstruction include **computer-assisted surgery (CAS)** with **virtual surgical planning (VSP)** using CT scans, **intra-operative imaging and navigation**, and **patient-specific implants (PSIs)**.

CAS facilitates real-time guidance during surgery, while navigation helps visualize surgical outcomes during surgery, enabling the correction of sub-optimal fracture reduction and positioning of implants. PSIs offer precise intra-operative implant positioning, improving post-surgical outcomes (1).

3.3. Three-dimensional (3D) printing

3D printing, also known as additive manufacturing (AM) or rapid prototyping, refers to a process of creating a physical object from a 3D digital model, typically by laying down or solidifying a material layer by layer in succession (25). Charles Hull introduced this technology in 1986 using a process known as stereolithography (SLA), which involves the solidification of layers of photopolymer resin[3] (26,27).

The role of 3D printing in healthcare and clinical practice is expected to be significant, as it offers the opportunity to create customized devices designed for the complexity and individual variances within patient populations (28). For decades, 3D printing has been used for rapid prototyping. However, recent advances in the available materials, speed, resolution, accuracy, reliability, cost and repeatability have significantly broadened the clinical applications of 3D printing technologies. Many medical fields are already using 3D printing to manufacture custom surgical tools, guides, implants, external prosthetics, devices for pre-operative planning, and educational models. The customization of patient-specific devices is expected to reduce surgical time while increasing the accuracy and success of the outcome (28–30).

3.3.1. Overview of additive manufacturing (AM) technology

3.3.1.1. Materials

A diverse range of materials can be 3D printed as a result of fast development in AM technologies. Materials in the forms of filaments, wire, powder, paste, sheets and inks can be used for 3D printing. In the medical field, the most commonly used materials for fast prototyping are **thermoplastic polymers** like polylactic acid (PLA) and **thermosetting powders** such as photopolymer resins (26).

[3] Photopolymer resin is a polymer that changes its properties when exposed to light, most commonly ultraviolet light. A polymer is a substance with a molecular structure composed of a large number of similar units bonded together.

3.3.1.2. Techniques

AM technologies can be classified in six different processes (27):

- **Binder jetting**: Liquid solutions are extruded from a printhead and deposited onto a powdered bed. The droplets infiltrate the powdered bed, resulting in material crosslinking, followed by the introduction of a new layer. This technique offers advantages such as low material costs and the ability to print in color. However, its major drawbacks include low-resolution, unset powder, and low compressive strength. Binder jetting is primarily used for creating anatomical study models (31).

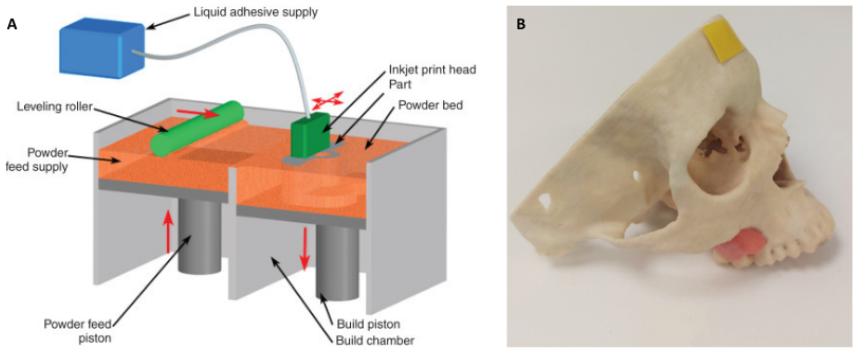


Figure 8. A) Diagram illustrating the binder jetting 3D printing process. B) 3D printed model fabricated by a multi-coloured binder jetting 3D printer. Images extracted from: A) (32) and B) (27)

- **Directed energy deposition**: A high-energy electron beam selectively melts and fuses the desired metal on a build platform, upon which new material is deposited via a nozzle. This technique offers speed with high temperatures, allowing the fabrication of extremely dense products with controlled porosity, such as custom titanium plates. However, both the technology and materials are costly, and the fabrication process generates airborne particles, making it a less popular choice for medical applications (33,34).

- **Material extrusion**: A material is dispensed in a controlled manner from a printhead, typically equipped with a heating apparatus, onto a build platform. This technology offers high-porosity products with variable mechanical strength, depending on the chosen material and print settings. However, material

extrusion has limitations, including a narrow diversity of print materials (mainly thermoplastic polymers) and limited interlayer bonding. In clinical practice, this technique is primarily used to generate anatomic models (35).

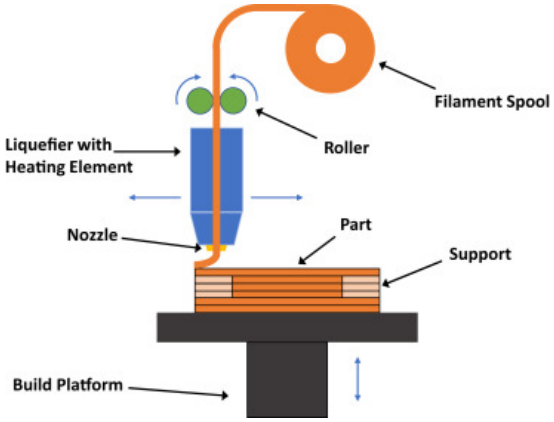


Figure 9. Diagram illustrating the material extrusion 3D printing process. Image extracted from (36)

- **Material jetting**: A curable medium[4], such as photopolymers, is jetted onto a build platform via an inkjet printhead. This material is cured layer-by-layer while the platform is constantly lowered. This methodology provides high accuracy and smooth surfaces in a relatively fast and uncostly process. Nevertheless, the dispensed materials are expensive and messy, and can cause irritation to living tissues. Therefore, its primarily application is for dental models (37).

- **Powder bed fusion**: A powdered medium, such as titanium or metal alloys, is dispensed onto a build platform, and then subjected to intense and focused heating, which bonds the powder particles. The use of lasers makes the process highly accurate, and the end products are autoclavable and can be rapidly produced. However, the disadvantages are the heavy infrastructure required for the manufacturing process, and the high cost of the technology. This methodology has been applied to produce dental prosthesis and implants (38).

[4] "Curable medium" refers to a material that can undergo a curing process to change its physical properties. In the context of 3D printing, it typically involves materials that can be solidified when exposed to a specific stimulus, such as light or heat. The curing process transforms the material from a liquid or gel state to a solid state, contributing to the formation of the final 3D printed object.

- **Vat polymerization or SLA**: A photosensitive polymer solution within a container or chamber is cured using a light source. The process is fast and enables the fabrication of extremely complex constructs with high accuracy. It has proven to be suitable for dental models and surgical guides. However, the resins used can be messy and, for the most part, not biocompatible, resulting in end products with a limited shelf life (27).

3.3.2. 3D printing in Oral and Maxillofacial (OMF) surgery

The use of 3D printing in OMF surgery began approximately 30 years ago with SLA anatomic models used for surgical planning. However, until recently, its fabrication remained in the hands of the industry (39). Over the past decade of general use, the availability of low-cost 3D printers has revived surgeons' interest in this technology. Applications have expanded significantly, going from anatomic models to PSIs, including cutting or drilling guides (40).

3.3.2.1. In-house or 3D printing Point-of-Care (3DP PoC)

In the last few years, the integration of **3DP PoC facilities** into healthcare centers has become more common, especially in some of the world's top-ranked hospitals (41). A 3DP PoC facility is a physical infrastructure located near the treatment site of patients (hospitals, dental laboratories, surgical facilities) in need of custom-fabricated medical devices and implants (42). 3DP PoC laboratories are equipped with infrastructure that usually includes 3D printers, post-processing equipment and appropriate software that enables the digitalization of medical images into 3D models. The establishment of these facilities can bring 3D printing closer to OMF surgeons, facilitating its integration into daily practice and contributing to optimal clinical outcomes, team learning and increased efficiency (27,43,44).

The term **"in-house"** refers to having the 3D printer within the hospital's own facilities, allowing the immediate availability of models in time for surgery (45).

In *Figure 10*, the workflow of a 3DP PoC facility in an OMF unit is schematized.

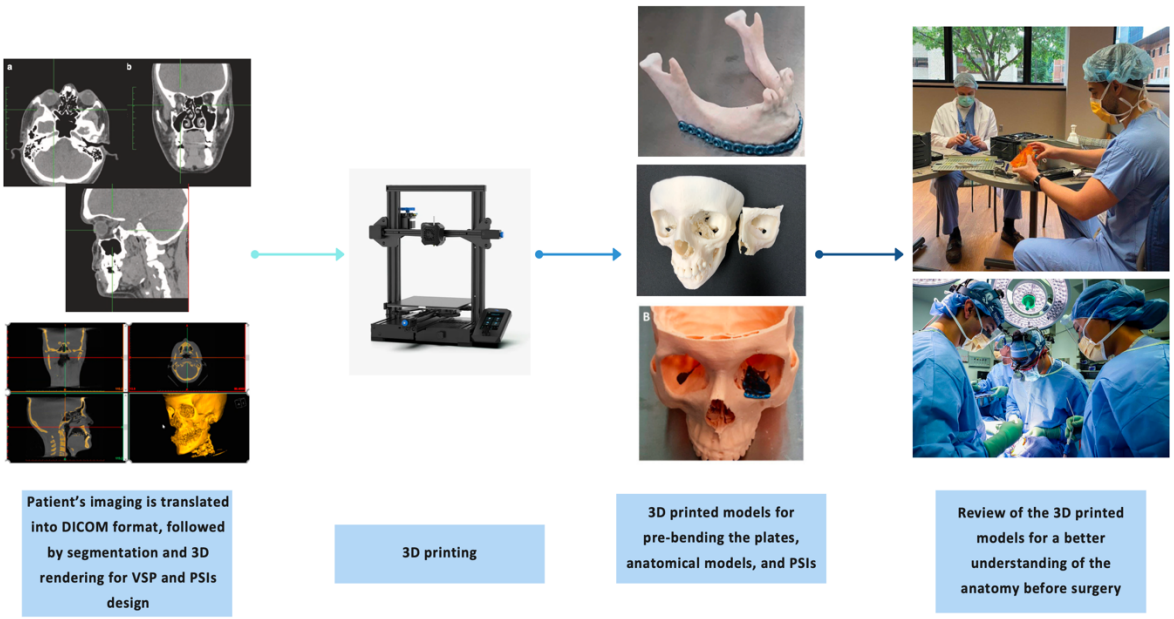


Figure 10. Diagram illustrating the workflow of a 3DP PoC facility, from the image acquisition to the surgical procedure. Adapted from (27)

Following the acquisition of patient imaging, medical data are obtained in Digital Imaging and Communications in Medicine (DICOM) format and segmented using specific software, such as 3D Slicer v5.6.1. This software aids in delineating the bone regions of interest from 2D section, later to be interpolated into a 3D object. Once the segmentation process is completed, a 3D model in Standard Triangulation Language (STL) data format is extracted from patient images. This model can be either 3D printed or further designed as a template for guides or PSIs (27). Subsequently, the OMF surgical team can study the patient's anatomy using the 3D printed anatomic model. They can pre-bend the implants into the anatomic model for reducing fractures or directly use the PSIs during surgery.

3.3.2.2. Clinical applications

Addressing the complexity of facial skeleton reconstruction, repair of facial asymmetry, restoration of orbital volume, and enhancement of aesthetics and functional performance can be challenging. Therefore, the use of 3D printing technologies can provide crucial support to OMF surgeons in achieving better outcomes.

In the field of OMF surgery, 3D printing technologies have made a significant impact in four major areas, one of them being **facial trauma** (27):

- **Mandibular fractures**: 3D printing is used to create anatomical models for pre-bending fixation plates or producing custom plates based on VSP. This approach minimizes post-operative complications and reduces operative time (46,47).

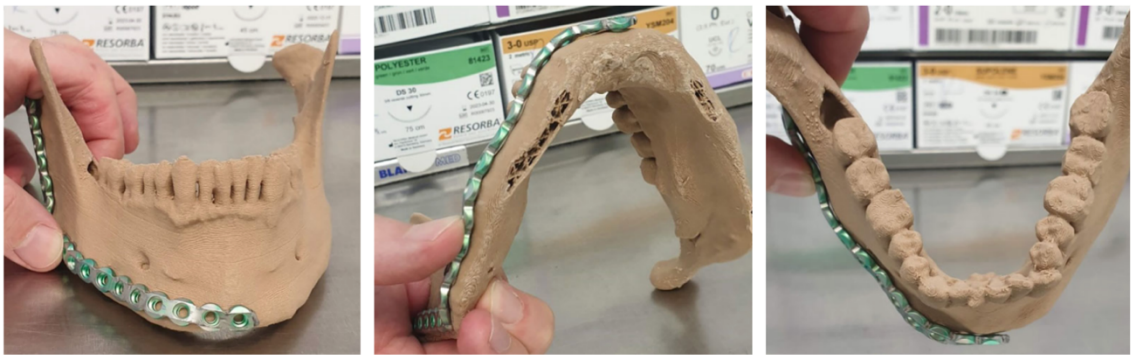


Figure 11. 3D printed mandibular models and pre-bending of the fixation plates. Images extracted from (48)

- **Midface and Zygomatic complex trauma**: Involves a similar workflow, using anatomical models for pre-bending fixation plates. VSP-based design of PSIs for fragment reduction can also be extremely beneficial in these cases (49,50).

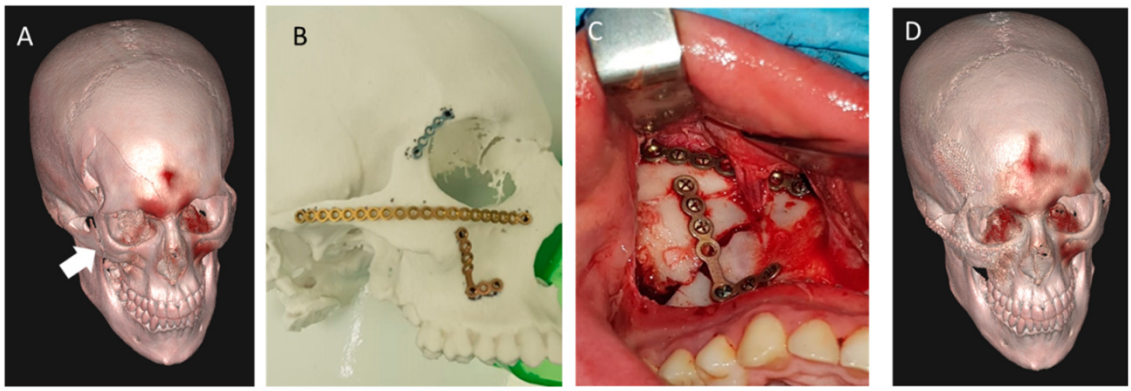


Figure 12. 3D design and printing for midface reconstruction. A) Volumetric representation of a zygomatic complex fracture (white arrow). B) Mirroring and pre-bending reconstruction plates on the 3D printed model. C) Intra-operative installation of pre-bended implants. D) 3D visualization of the post-operative results. Images extracted from (27)

- **Orbital reconstruction**: Following similar treatment protocols, with pre-operative 3D evaluation of the anatomy and pre-bending of titanium meshes. This method facilitates the surgical process, as the implant can be pre-selected

and adapted to each patient, ultimately reducing surgical time (51). Another methodology involves mirroring the intact contralateral orbit instead of the fractured one, which is subsequently 3D printed and used for pre-bending. The mirrored orbit can serve as the basis for VSP and PSI design (52,53).

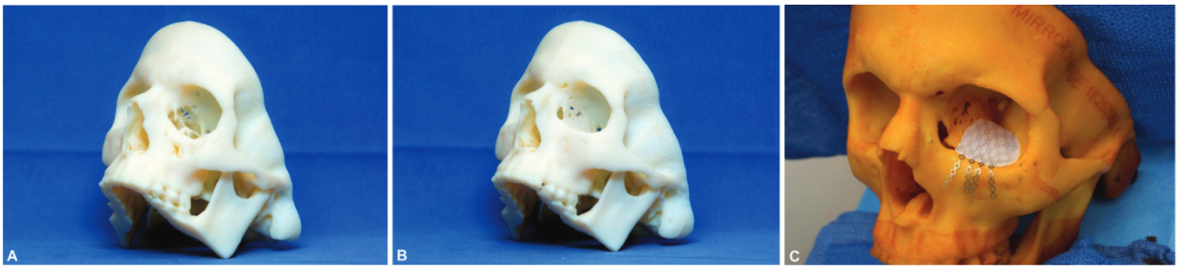


Figure 13. Left orbital floor fracture 3D printed model. A) Printed 3D model of the fracture. B) Printed 3D model created by mirroring the normal right orbit onto the left side. C) Printed 3D model used intraoperatively to contour the orbital floor implant. Images extracted from (44)

The other three major areas in OMF surgery that utilize 3D printing technologies are **orthognathic surgery**, maxillofacial **tumor resection and reconstruction**, and **total joint replacement** (27). The following figures show some example applications.

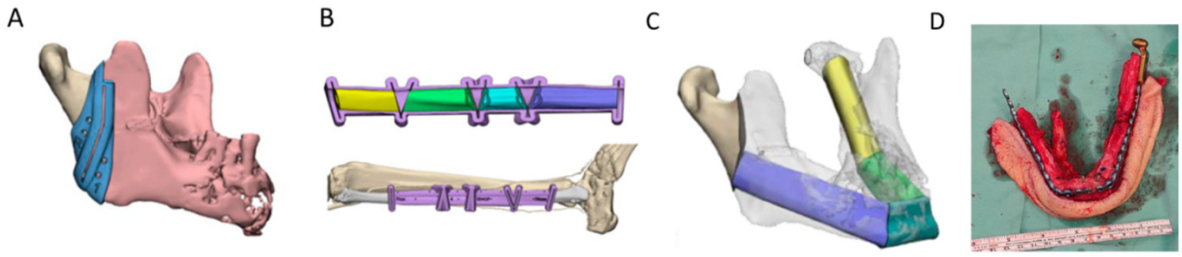


Figure 14. 3D design and printing for mandibular reconstruction using the fibula-free flap. A) and B) Osteotomy guides for both the cancerous lesion (pink area) in the mandible and the fibular tissue harvest designed based on the patient's anatomy. C) 3D VSP-based reconstruction of the mandible. D) Pre-bending of the reconstruction plate onto the harvested fibular flap. Images extracted from (27)

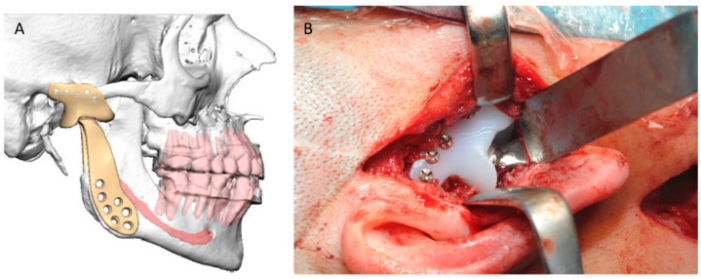


Figure 15. 3D-based total joint replacement. A) VSP. B) Intra-operative placement of the PSI to the mandible and fossa. Images extracted from (27)

3.3.2.3. Educational purposes

3D printing models offer an additional platform for **surgeons, residents and students' surgical education**. These models serve as reusable visual teaching aids to enhance hands-on learning experiences. They have been shown to stimulate interest and curiosity, and enhance visual-spatial skills by providing immediate feedback, improve memory of procedures, and allow for preparation with realistic models prior to the day of the surgery (44,54,55). Having haptic feedback with the 3D model gives the surgeon a better sense of the fracture and the anatomical conditions, resulting in better performance in the operating room (48,56).

Specifically, in the teaching of orbital anatomy, the use of 3D printed models is especially helpful as orbital anatomy is complex and there is a restricted field of view during surgery that makes intra-operative teaching difficult. Vatankhah et al. performed a study in which 24 ophthalmology residents were randomized into two groups of learning. One group trained with traditional methods and the other group with 3D printed models of fractures. The study concluded that the teaching method using 3D printed models had a positive effect on the trainee's visual and perceptive competencies as well as the whole learning process (54).

Furthermore, using 3D models for **communication with patients** before surgery provides a valuable tool for enhancing patient understanding and engagement (57). These anatomic models enable surgeons to explain complex surgical procedures, expected outcomes, and potential challenges in a more accessible and comprehensible manner. Patients can visually appreciate the planned intervention. Ultimately, utilizing 3D models for communication encourages a collaborative and informed approach to treatment. It helps patients to adhere better to the treatment when compared to conventional methods such as radiological image demonstration and drawing a sketch of the surgical access way (56).

4. JUSTIFICATION

Fractures involving the orbital floor constitute around 40% of all facial fractures. Among these, isolated orbital floor fractures specifically represent 4-16%. The increased occurrence is primarily attributed to the specific anatomy of the orbital floor, which features one of the thinnest walls measuring 2 mm in thickness (2). These fractures are more common in male individuals in the second and third decade of life, causing potential sequelae in young adults (58). Considering this, it is paramount that these surgical procedures are successful, due to the potential loss of productive years of life.

One potential consequence following reconstructive surgery for orbital floor fractures is persistent enophthalmos, which can have both aesthetic and visual repercussions. Aesthetic concerns arise from the asymmetry in eye position, while visual implications result from disparities in globe position and projection between the two eyes, leading to binocular diplopia (23). Under normal viewing conditions, each eye sends a slightly different image to the brain, and cortical fusion mechanisms integrate these images, utilising the slight disparity between them to create the illusion of 3D vision. If the images sent to the brain are too different due to misalignment of the eyes, diplopia results (59). Another potential sequela is infraorbital nerve dysfunction, attributable to its proximity to the orbital floor. This dysfunction may manifest as paraesthesia or even anaesthesia throughout the lower eyelid, midface, upper lip, and gums.

In the OMF surgery field, the integration of personalized medicine and in-house 3D printing stands as a pioneering approach. This innovative methodology allows for the creation of individualized anatomic models, derived from patients' pre-operative CT scans, offering a detailed representation of the unique fracture characteristics. Tailoring devices and procedures to the patient is expected to reduce the time required for surgery, treatment, or recovery, while increasing the accuracy and success of the outcome (28). 3D printed objects provide the tactile quality, enabling surgeons to study complex cases, practice procedures, and educate students and patients (60,61). Moreover, incorporating 3D models for pre-operative communication offers a valuable resource to improve patient understanding and satisfaction (57).

Studies into cranial fractures, particularly orbital fractures, have documented enhanced outcomes attributed to the utilization of 3D printed anatomical models as guides before and during surgery. These models serve to improve the understanding of the fracture and mitigate potential risks. They can also play a crucial role in shaping the titanium mesh before surgery, leading to a better fit and reduced surgical duration (61), consequently lowering the risk of surgery-related complications such as infections (28).

Given the anatomical challenges and potential consequences associated with orbital floor fractures, this study aims to investigate whether integrating an individualized 3D printed anatomical model into pre-operative planning reduces the occurrence of persistent enophthalmos, in comparison to conventional pre-operative planning, which would consequently imply an improvement in visual function and aesthetic.

5. HYPOTHESES

5.1. Main hypothesis

The utilization of in-house 3D printed anatomic models for pre-operative planning, compared to conventional pre-operative planning, **reduces the occurrence of persistent enophthalmos** in isolated orbital floor fractures, measured one month after surgery.

5.2. Secondary hypotheses

- The utilization of in-house 3D printed anatomic models for pre-operative planning, compared to conventional pre-operative planning, will lead to a **decreased occurrence of post-operative complications**, including persistent diplopia, infraorbital nerve dysfunction, and restricted EOM motility, in isolated orbital floor fractures, measured one month after surgery.

- The integration of 3D printed anatomic models into pre-operative planning, compared to conventional pre-operative planning, will **improve patients' understanding and satisfaction with the information received about their treatment process**, in isolated orbital floor fractures.

6. OBJECTIVES

6.1. Main objective

To investigate whether the utilization of an in-house 3D printed individualized anatomic model for pre-operative planning in isolated orbital floor fractures compared to conventional pre-operative planning**, reduces the occurrence of persistent enophthalmos** measured with a Hertel exophthalmometer one month after surgery.

6.2. Secondary objectives

- To investigate and compare the **presence of post-operative complications** such as persistent diplopia, infraorbital nerve dysfunction, and restricted EOM motility, between the two pre-operative planning methods, in isolated orbital floor fractures, one month after surgery.

- To assess and compare the level of **patients' understanding and satisfaction with the information received about their treatment process** between the two pre-operative planning methods in isolated orbital floor fractures.

7. MATERIALS AND METHODS

7.1. Study design

This study will be carried out as a multicentric, prospective, randomized, open-label clinical trial.

7.2. Study setting

This protocol is designed to be multicentric, including reference hospitals from Catalonia, all of which belong to Institut Català de la Salut (ICS). All hospitals with an OMF surgery unit will receive invitations to participate. Accordingly, the following hospitals are asked to participate in the study (*hospital catchment area in brackets*):

- Hospital Universitari Doctor Josep Trueta (*800.000*)
- Hospital Universitari Germans Trias i Pujol (*800.000*)
- Hospital Universitari Vall d'Hebron (*430.000*)
- Hospital Universitari de Bellvitge (1.*201.192*)
- Hospital Universitari Joan XXIII de Tarragona (*600.000*)
- Hospital Universitari Arnau de Vilanova de Lleida (*450.000*)

The main project coordinator for this trial will be Hospital Universitari Doctor Josep Trueta de Girona (HUJT). A researcher from each hospital will be assigned as the representant to facilitate effective communication and coordination among all participant hospitals.

7.3. Population

The study population will include individuals aged 18 years or older presenting with an isolated orbital floor fracture requiring surgery.

7.4. Study subjects

7.4.1. Inclusion and exclusion criteria

Table 4. Inclusion and exclusion criteria

INCLUSION CRITERIA

- 18 years or older
- Isolated orbital floor fracture
- Fracture requiring surgery (1,4,16):
  ○ Acute injury to the orbit with enophthalmos (>2mm) and/or hypophthalmos
  ○ Severe restriction of ocular motility with CT-evidenced muscle entrapment or incarceration of periorbital soft tissue
  ○ Defects of the orbital floor larger than 50% of the orbital floor area or greater tant 20 x 20 mm in size
  ○ Diplopia that is non-resolving and persistent for more than 2 weeks due to entrapment or fibrosis of orbital soft tissue

EXCLUSION CRITERIA
- Polytrauma patients or multiple fractures - Fractures requiring urgent surgical intervention within 24 hours - Presence of retrobulbar hemorrhage - Surgery is contraindicated (2):   ○ Hyphema, retinal tears, globe perforation, patient with monocular vision, medical instability - Pregnancy - History of enophthalmos before trauma - History of diplopia, restricted EOM motility and/or infraorbital nerve dysfunction before trauma - Individuals who are unwilling to participate in the study

7.5. Sampling

7.5.1. Sample selection

A non-probabilistic consecutive sampling method will be followed in the OMF Surgery Department of each participant hospital.

All patients who meet the inclusion criteria and none of the exclusion criteria will be offered to participate in the study.

7.5.2. Sample size

The sample size has been estimated using GRANMO v7.11 software, specifically the setting for two independent proportions.

Accepting an alpha risk of 0,05 and a beta risk of 0,2 in a two-sided test, a total of **132 subjects (66 in each group)** will be necessary to find a statistically significant proportion difference of 20% or more. This calculation is based on the expectation that the proportion in the control group will be 70%, and in the intervention group, it will be 90%. A drop-out rate of 10% has been assumed.

This assumption has been made based on the expertise of the OMF surgical unit in HUJT.

7.5.3. Randomization and masking techniques

Participant patients will be assigned a numerical code (numbers from 1 to 132). Afterwards, to reduce the bias of selection, a software will be used to distribute patients into the two groups in a 1:1 ratio. The study groups will be:

- **Intervention group** (Group A): Pre-operative planning method using in-house 3D printed models.
- **Control group** (Group B): Conventional pre-operative planning method.

The study is designed as an open-label clinical trial, where both the patient and the OMF surgeon are aware of the pre-operative planning method. Due to the nature of the study, blinding is not feasible. To minimize detection bias, outcomes will be evaluated

by a blinded independent physician (a different OMF surgeon who is not involved in planning or performing the surgery). Additionally, the independent statistician will remain unaware of the pre-operative planning method used for each participant patient.

7.5.4. Estimated time of recruitment

This clinical trial is designed to be multicentric. Considering the number of patients scheduled for an isolated orbital floor fracture surgery in HUJT (15 patients per year), we estimate **1 year and 8 months** of recruitment will be necessary to be able to enroll the required number of patients (132 patients) across all the participant hospitals.

7.5.5. Participant withdrawal or termination

All participant patients will have the autonomy to withdraw from the study at any time. Those choosing to withdraw must communicate their decision to the research team. Additionally, participants will be considered to have dropped out of the study if they fail to attend the scheduled follow-up visits. Patients who meet exclusion criteria, whether newly developed or initially unrecognized, will also be excluded from the study.

In the event of withdrawal, additional patients will not be recruited in the clinical trial to replace the withdrawn participants.

7.6. Variables

7.6.1. Independent variable

The independent variable of this study refers to the type of **pre-operative planning procedure**.

- Intervention group (Group A): Pre-operative planning using in-house 3D printed models.
- Control group (Group B): Conventional pre-operative planning method.

7.6.2. Dependent variables

Main dependent variable

- **Persistent enophthalmos**: Enophthalmos is defined as the posterior displacement of the eye globe in an anteroposterior plane within the orbit (62). Enophthalmos will be measured using a **Hertel exophthalmometer** (*see Measurement Tools*) one month after surgery and categorized as a dichotomous yes/no variable. Enophthalmos will be diagnosed when there is a difference of **more than 2mm** between both eyes (24).

Secondary dependent variables

- **Post-operative complications**: Complications such as persistent diplopia, infraorbital nerve dysfunction, and restricted EOM motility are known to impact patients' recovery. In this study, post-operative complications will be evaluated one month after surgery and categorized as a dichotomous yes/no variable.

- **Patient understanding and satisfaction with the information received about their treatment process**: It is important for the patient to comprehend the treatment they will undergo and for their concerns to be addressed. This variable will be evaluated with three items: understanding of the fracture's location, understanding of the surgical procedure, and overall satisfaction with the information received. These items will be measured using a Visual Analogue Scale (VAS) (*see Measurement Tools*), with values ranging from 0 to 10.

All variables will be recorded in the patient's clinical chart and in the Research Electronic Data Capture (REDCap) database.

7.6.3. Covariates

- **Age**: Expressed in years, at the time of the fracture treatment. The information will be collected from the ID card or any official document.
- **Sex**: Categorized as a male/female covariate. It will be extracted from the ID card and understood as the chromosomal sex, even though we assume that gender identification can be different from the chromosomal sex.
- **Ethnicity**: Categorized in five groups between African, Asian, Caucasian, Latin-American and Others.
- **Socioeconomic status**: Categorized in social classes from I to V based on patient's education level and occupation according to Domingo et al (63).
- **Smoking**: Categorized in three groups between Non-smokers, Smokers (considering individuals who smoke at the time of the diagnosis or on its 6 months prior) and Ex-smokers (considering those who smoked during their life but have not smoke during the past 6 months).
- **Alcohol consumption**: Categorized in three groups between Non-consumers, Moderate consumers (20-40g/day in women and 50-60g/day in men) and High consumers (>40g/day in women and >60g/day in men).
- **Concomitant diseases or disorders**: Categorized as a dichotomous yes/no covariate. If answered "Yes" the patient will be asked to indicate which ones among neurological disorders, chronic infectious diseases, metabolic disorders, cardiovascular disorders, or others (specify in case of doubt).
- **Duration from injury to repair**: The optimal time for isolated orbital wall fracture surgery is within 4,5 to 7 days after the trauma to prevent diplopia and limitations in EOM movement (64,65). It will be categorized as a quantitative continuous covariate and expressed in days.
- **Hospital**: Despite the controlled and clear explanation of the protocol, and the training sessions before starting the clinical trial, the multicentric nature of the study may lead to subtle variations in the process across hospitals. This covariate will be categorized into six groups between HUJT, HUVH, HUB, HUGTP, HUJ23 and HUAV.

All covariates will be recorded in the patient's clinical chart and in the REDCap database. Study variables and covariates can be seen in *Table 5*.

Table 5. Study variables and covariates

VARIABLES AND COVARIATES		MEASUREMENT TOOL	TYPE OF DATA	CATEGORIES / VALUES
Independent variable	Type of pre-operative planning procedure	Patient's clinical chart	Qualitative	Type of pre-operative planning method
Main dependent variable	Persistent post-operative enophthalmos	Hertel exophthalmometer	Qualitative	Yes / No
Secondary dependent variables	Post-operative complications	Patient's clinical chart	Qualitative	Yes / No
	Patient understanding and satisfaction with the information received	VAS	Quantitative discrete	Scale from 0 to 10
Covariates	Age	Patient's clinical chart	Quantitative continuous	Number of years
	Sex		Qualitative	Male / Female
	Ethnicity		Qualitative	a. African b. Asian c. Caucasian d. Latin-American e. Other
	Socioeconomic status		Qualitative	Class I to V (63)
	Smoking		Qualitative	a. Non-smokers b. Smokers c. Ex-smokers
	Alcohol consumption		Qualitative	a. Non-consumers b. Moderate consumers c. High consumers
	Concomitant diseases or disorders		Qualitative	Yes / No
	Duration from injury to repair		Quantitative continuous	Number of days
	Hospital		Qualitative	a. HUJT b. HUVH c. HUB d. HUGTP e. HUJ23 f. HUAV

7.7. Intervention

All patients requiring surgery for an isolated orbital floor fracture who meet the inclusion criteria will be informed about the study. Afterwards, the OMF team will provide the patient with the Information Form (*see Annex 1*) and the Informed Consent Form (*see Annex 2*).

Patients will be randomly assigned to two groups: the **intervention group** (Group A) and the **control group** (Group B). For Group A, the OMF surgical team will conduct pre-operative planning using an in-house 3D printed model based on the patient's specific anatomy and fracture characteristics, derived from their pre-operative CT scan. For Group B, the conventional pre-operative planning method will be followed.

7.7.1. Control group

The conventional diagnostic process and pre-operative planning of orbital floor fractures begins with an initial assessment, including the patient's history, and continues with a clinical and radiographic evaluation (5).

It is crucial to perform a thorough **clinical history**, including details of current illnesses and past medical and surgical events, to identify any relevant medical conditions, previous trauma, bone diseases, nutritional and metabolic disorders, and psychiatric conditions that might influence the timing and management of the fracture (66).

The second step involves **clinical evaluation**, which will be conducted by both an ophthalmologist and the OMF surgical team. A complete ophthalmologic examination is essential for any patient presenting with periocular or ocular trauma. An 8-point ophthalmological examination will be followed (1):

1. Visual acuity: It will be assessed using a Snellen chart, evaluating the ability to read letters, count fingers, perceive hand movements, and detect light perception.
2. Pupillary examination: The size, shape, symmetry and direct/indirect reflex to light will be examined. Conditions such as glaucoma, previous ocular surgery, and injuries to the ocular system may contribute to anisocoria (unequal pupil size) or irregular pupils.

3. EOM motility and alignment: The patient will be screened for all the diagnostic gaze positions (*see Introduction*). Any diplopia and restrictions of gaze will be noted.
4. IO pressure: Tonometry will be conducted using a Goldmann applanation tonometer. The normal IO pressure ranges between 10 and 21 mmHg.
5. Visual fields: Each quadrant will be assessed by confrontation[5], asking the patient to count the number of fingers held up by the examiner.
6. External examination: The examiner will assess for clinical exam findings common in orbital trauma, including periorbital edema, periorbital ecchymosis, subconjunctival hemorrhage, contusions or hematomas, subcutaneous emphysema with crepitus, lacerations involving the eyelids, injuries to the canthal apparatus, and neurological deficits of the infraorbital nerve.
7. Fundoscopic examination: It will be assessed using an ophthalmoscope to assess the retina, optic nerve head, and vessels. It will also provide information about the presence of IO hemorrhages or foreign bodies.
8. Globe position: The evaluation will be performed both clinically and using the Hertel exophthalmometer. Inferior displacement of the globe may be observed after a large orbital floor fracture. Exophthalmometry measurements may reveal enophthalmos on the side of the fracture. Enophthalmos may not be present in the acute setting due to edema, hemorrhage, or both. Exophthalmometry measurements can even show exophthalmos (5).

The OMF surgical team will conduct a facial examination of the orbital and periorbital area. The evaluation will include bilateral palpation comparing both infraorbital and lateral rims and zygomatic arches, searching for steps or bone asymmetries (13). The EOM motility will be checked again to confirm or rule out muscle entrapment.

Once the history and clinical examination are finished, the clinician will perform a **radiographic examination**. A CT scan without contrast is the imaging gold standard in

[5] The patient covers their right eye with their right hand (vice versa when testing the opposite eye). With the examiner seated directly across from the patient, the patient directs their gaze to the corresponding eye of the examiner. A moving target (examiner's fingers) starts outside the usual 180º visual field, then moves slowly to a more central position until the patient confirms visualization of the target.

the trauma setting to assess orbital and facial fractures. Coronal views and thin cuts (0,5-2 mm) are recommended to provide sufficient detail of the orbits. Changes in the shape of rectus muscles on coronal views are useful to assess for traction on periorbital soft tissues and muscle. The displacement of orbital bones is best assessed in the bone window, whereas orbital soft tissue herniation and muscle entrapment can be best evaluated in the soft tissue window. It is important to determine the extent of bone displacement on imaging, as a larger orbital floor fracture with greater displacement of orbital tissues will more likely result in enophthalmos and require surgical repair. Other findings on imaging in the setting of an orbital floor fracture may include opacification of the maxillary sinuses and displacement of the globe (5).

After completing the initial assessment, the OMF surgical team will review the entire set of tests to determine the most appropriate course of action.

7.7.2. Intervention group

In the intervention group (Group A), the same pre-operative process as in the control group will be followed, with the additional step of creating an in-house 3D printing model of the patient's fracture. The 3D printing process will be carried out by a 3D printing technician.

The workflow of each case will begin with adequate, high-resolution imaging extracted from the pre-operative CT scan. CT scan cuts will have a thickness of 0.5 mm because it has been reported that acquisition with a voxel[6] size above 1.00mm may be suboptimal for the purpose of 3D design due to compromised resolution (27).

After imaging, medical data will be obtained in DICOM format and segmented using **3D Slicer v5.6.1 software** to delineate the region of interest from 2D sections, later to be interpolated into a 3D object. This can be achieved automatically, manually or through a combination, depending on image contrast.

[6] Short for "volumetric pixel". The smallest identifiable unit in a 3D space. In medical imaging, voxels are used to create detailed 3D representations of objects or structures.

After additional processing, such as noise removal or defect correction, an STL file is extracted from patient imaging. From this file, the 3D model is printed.

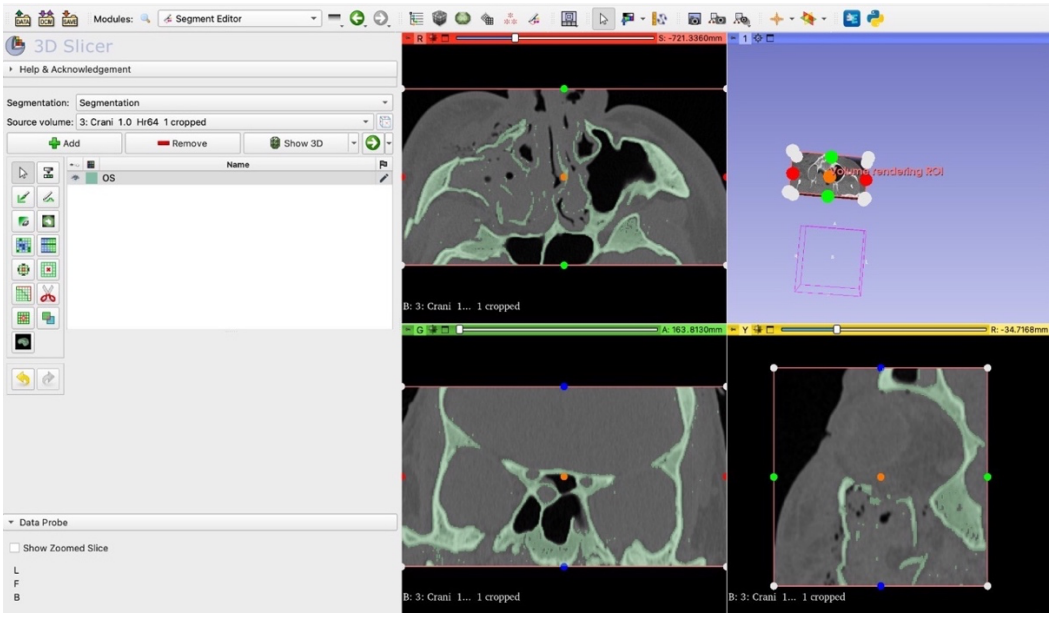


Figure 16. 3D Slicer v5.6.1 software used for image segmentation showing a CT scan of an orbital fracture. Image taken by Alba Rodríguez.

Subsequently, this STL file will be processed using **Ultimaker Cura v5.6.0 software** which will be connected to the in-house 3D printer. This software is used for specifying characteristics such as printing quality (in this protocol, it will be "Standard Quality – 0.2 mm") and the utilization of supports to prevent model tipping during printing (45).

In this protocol, a **Creality Ender-3 V2 3D printer** will be used following the material extrusion technology. It is a common form of 3D printing in which a material or polymer is dispensed from a printhead that usually contains a heating apparatus onto a build platform. This technology is mainly used to generate anatomic models (27,35). In this protocol, a biodegradable and recycled PLA will be used as the printing material, with a diameter of 1.75 mm and a standard 0.4 mm print nozzle.

The 3D printing process will involve creating the **anatomic model of the patient's orbital floor fracture and its mirroring**. The mirroring technique consists of printing the intact contralateral orbit but positioned in the place of the fractured orbit (27).

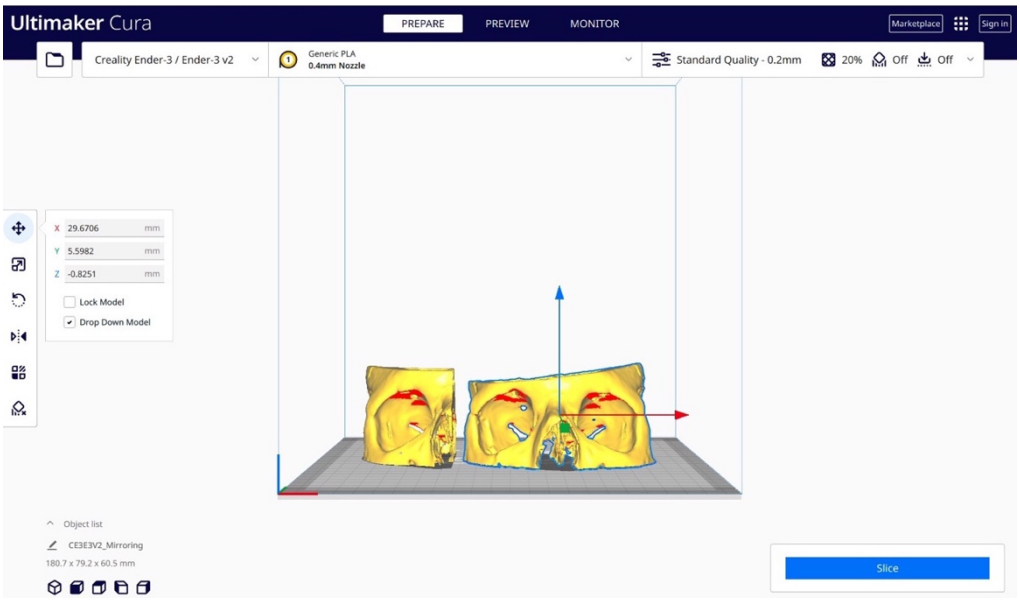


Figure 17. Ultimaker Cura v5.6.0 3D software showing an orbital fracture model and its mirroring before being printed. Image taken by Alba Rodríguez.

Once the printing process is completed, approximately 8 hours later, printing supports will be removed. Subsequently, a visual quality check will be conducted by the 3D technician and the OMF team to identify any defects from lack of filament during the print (45).

Finally, the personalized 3D printed models will be utilized for evaluating the **pre-operative planning**. Each patient's fracture and anatomy will be carefully observed, and any atypical characteristics or anatomical defects will be studied. The haptic feedback provided by the 3D printed models will allow the OMF team to become more familiar with the anatomy and prepare for potential complications, thereby enhancing their ability to precisely fix the fracture (48,51).

The 3D printed models will also play an important role in pre-bending the orbital implant, as shown on *Figure 18*. In the reconstruction of the orbital floor fracture, a titanium mesh plate will be used. The mirroring model will serve as the basis for pre-bending this titanium mesh plate, which will be hand-molded to precisely fit the size of the defect. Once contoured, the implant will undergo sterilization in an autoclave following a standardized and certified sterilization procedure (67). A **transconjunctival approach** to the orbital floor will be followed in both the control and intervention group.

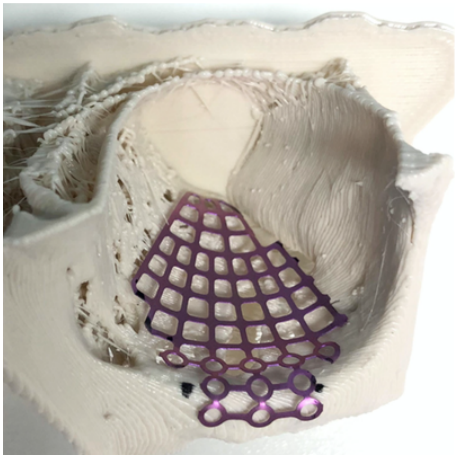


Figure 18. Orbital floor titanium mesh plate on a PLA 3D printed model. Extracted from (67)

7.8. Measurement tools

7.8.1. Equipment

- **Hertel exophthalmometer**: It is a handheld instrument with two identical measuring devices (one for each eye), connected by a horizontal bar. The distance between the two devices is adjusted by sliding one towards the other. When aligned correctly, the set of mirrors reflect a lateral image of each eye along with a measurement scale calibrated in millimetres (24). This measurement tool will be used to assess the primary dependent variable of the study, which is persistent enophthalmos.

Figure 19. Hertel exophthalmometry. Left panel shows the clinician sitting at eye level with the patient. The right panel shows a close-up view of the prism, the exophthalmometry reading is 17 mm. Extracted from (68)

7.8.2. Scales

- **Visual Analogue Scale (VAS)** (*Annex 3*): This scale uses a 10-point scoring system, where 0 points represents the worst and 10 points the best experience. In this study, VAS will be used to determine the overall satisfaction with the information received before surgery, the understanding of the fracture's location, and the understanding of the procedure.

7.9. Study circuit and data collection

The initial step in the study circuit involves diagnosing an isolated orbital floor fracture. Candidates to participate in the study will be identified from the emergency room of each participant hospital and/or derived from other hospitals that do not have an OMF surgical team.

The diagnosing process includes a detailed clinical history, an ophthalmological and facial examination conducted by both an ophthalmologist and an OMF surgeon, and a CT scan (*see Intervention*). Once the results are gathered, the OMF team will communicate the diagnosis to the patient and confirm that they meet the inclusion criteria while not meeting the exclusion criteria (*see Study Subjects*). Afterwards, the study will be explained, and the patient will be invited to participate.

After the study explanation, the OMF team will provide the patient with the Information Form and the Informed Consent Form (*see Annexes 1 and 2*), allowing enough time to read and address any questions or concerns. If the patient agrees to participate in the study, they will be required to sign the Informed Consent Form. A numerical code will be assigned to every participant patient to ensure anonymity. The physician will then register the covariates information in the patient's clinical chart.

The study's randomization will be performed (*see Randomization and Masking techniques*) dividing the participant patients into two intervention groups, A and B. In group A, the pre-operative planning will incorporate the in-house 3D printed model of the orbital floor fracture, while in group B, conventional pre-operative planning will be followed.

7.9.1. Before surgery

Prior to the surgical intervention, each patient will undergo **pre-operative planning** based on the randomization group assignment. In group A, the in-house 3D printed models will be processed and used to study the patient's anatomy and pre-bend the titanium mesh plate (*see Intervention*).

Later, patients will attend an anaesthesia visit and evaluation to ensure the safety of the surgery. During this visit, an OMF surgeon will thoroughly explain the patient's fracture location and the surgical procedure. In addition to the explanation, patients in group A will have the opportunity to visualize their fracture using the 3D printed models.

Afterwards, an independent physician will conduct an evaluation of the **patient's understanding and satisfaction with the information received**. As specified in *Variables*, this assessment will be measured using a VAS (*see Annex 3*) for understanding of the fracture location, understanding of the procedure, and overall satisfaction with the information provided. All answers will be registered in the patient's clinical chart and in the REDCap database.

Ultimately, patients will undergo surgery for the treatment of their isolated orbital floor fracture.

7.9.2. Follow-up

Once the surgery is completed, all patients will be hospitalized and checked daily for two days to ensure their maximum comfort. Evaluation of the patient's vision will be performed as soon as they are awakened by an ophthalmologist.

Following discharge, all patients will have scheduled for several **follow-up visits with an independent physician** (a different OMF surgeon from the one who performed the surgery). These visits will assess their status, check for the occurrence of persistent enophthalmos, and evaluate the presence of post-operative complications such as persistent diplopia, infraorbital nerve dysfunction and restricted EOM motility.

The **main follow-up visit** will take place **1 month** after the surgery, since the inflammation caused by the surgery will no longer be present. The independent physician will evaluate the presence of **persistent enophthalmos** using a Hertel exophthalmometer (*see Measurement Tools*). The Hertel measurement will be performed with the patient sitting upright, the patient's head in the primary position and the examiner's eyes at the same level as the patient's. The measurement will be taken in millimetres (mm) at the distance between temporal orbital rims, the deepest palpable point of the angle, and the apex of the cornea. Right eye readings will be taken before left eye readings without removing the instrument from the orbital rims (69). Normal distance from the orbital rim to the corneal apex can be seen in *Table 6*.

Table 6. Hertel exophthalmometer measures within the normal range in adults. Extracted from (24)

ETHNICITY	NORMAL DISTANCE (mm)
Asian	18
Caucasian	20
African	22

When a difference of **more than 2 mm** between both eyes is detected, enophthalmos will be diagnosed. The results will be registered in the patient's clinical chart and collected into the REDCap database.

Subsequently, the independent physician will examine whether the patient presents any of the post-operative complications considered in this study:

- **Persistent diplopia**: Diplopia is the simultaneous perception of two images of the same object in different positions (9). In this study, the independent physician will assess diplopia based on subjective reports of double vision in at least one direction of gaze, as done by Hsu et al. (70).

- **Infraorbital nerve dysfunction**: The infraorbital nerve is the terminal branch of the maxillary nerve. Before emerging on the face, the infraorbital nerve courses through the infraorbital canal on the orbital floor (71). This close association with

the orbital floor, makes it susceptible to injuries resulting from both trauma and the surgical process. The infraorbital nerve carries sensory information; its dysfunction affects the lower eyelid, cheek, side of the nose, upper lip, and upper teeth and gums ipsilaterally (9).

The independent physician will evaluate nerve dysfunction by using a cotton wisp to assess the patient's ability to feel light touch with their eyes closed. To evaluate pain and temperature, similar steps will be taken, but instead of the cotton wisp, a sharp pin and a cold tuning fork will be used (71).

- **Restricted EOM motility**: The EOM involve four rectus muscles and two obliques, which play a role in the different eye gaze positions (*see Figure 5*).

  The independent physician will instruct the patient to sit with the head up and looking straight ahead. Using a pen positioned about 40 cm in front of the patient's face, the examiner will move the pen in various directions, asking the patient to follow it without moving their head (72).

The evaluation results will be registered in the patient's clinical chart and collected into the REDCap database. The other follow-up visits will be scheduled at **2 weeks and 4 months** after the surgery, during which the same outcomes will be assessed.

A flow chart of the study circuit can be seen in *Figure 20*.

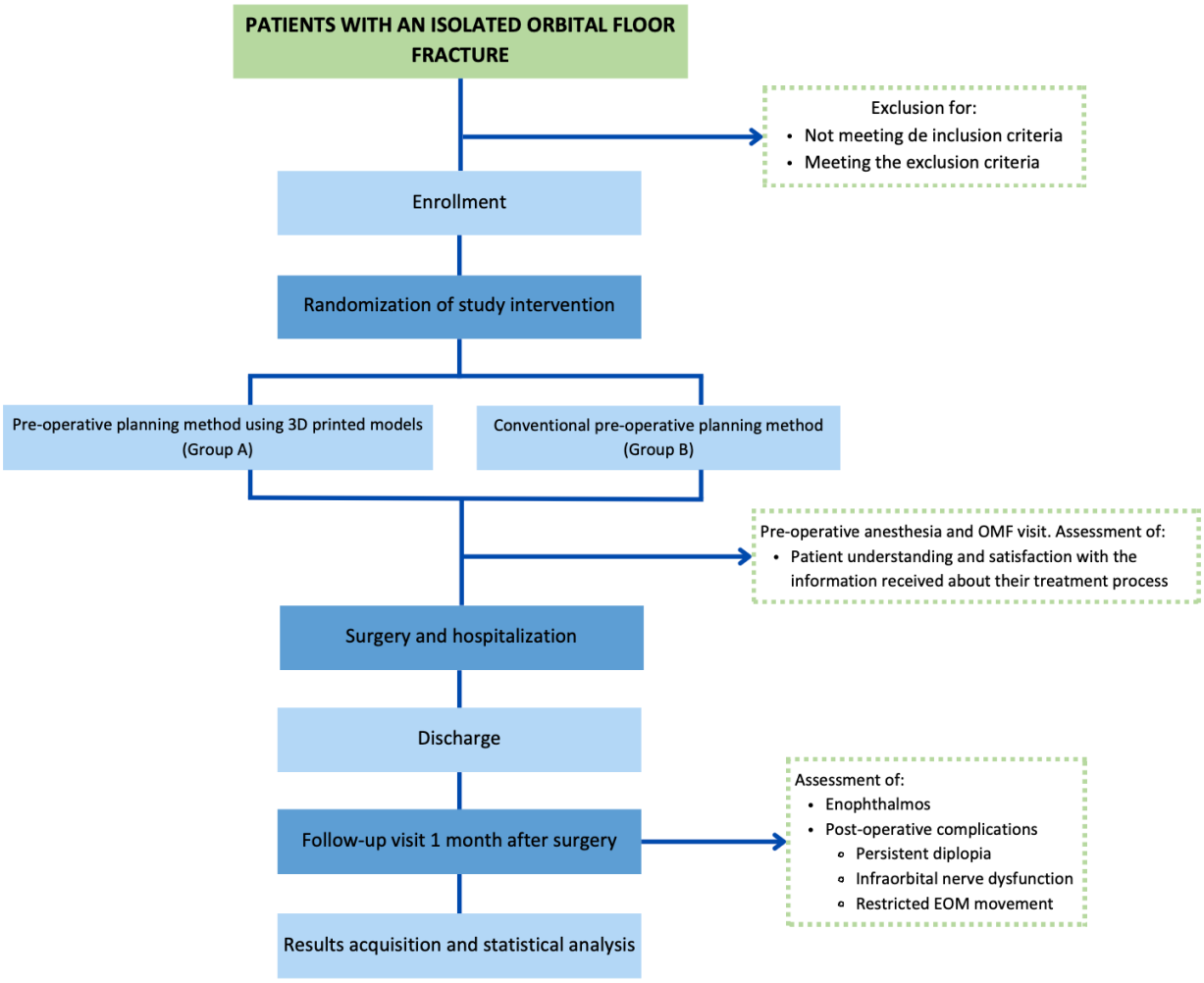


Figure 20. Participant flow chart through the study circuit

7.10. Safety

In this study, ensuring safety will be highly important to promote enthusiasm and trust in participant patients. The following measures will be implemented:

- **Equal surgical treatment**: Both randomized groups in the study will undergo the same surgical procedure, as the proposed intervention does not alter the intra-operative process. This surgical procedure has been extensively researched and is routinely used for the treatment of orbital floor fractures. Consequently, performing one pre-operative planning method or the other will not impact the patient's surgical treatment.

- **Control of post-operative complications**: Before signing the Informed Consent form (*see Annex 2*), the OMF surgical team will provide a detailed explanation of the potential complications associated with the procedure to all patients. The most common immediate complications following orbital surgery include edema, infection, wound dehiscence, and implant malposition. Late complications include persistent enophthalmos, persistent diplopia, neurosensory disturbances associated to the infraorbital nerve, and restricted EOM motility (1). It is important to emphasize that both groups will be equally exposed to the same surgical complications, as the procedure will be the same. Acute complications will be reported during the hospitalization post-operative period and the first follow-up visit, scheduled 2 weeks after surgery. Late complications will be reported during subsequent follow-up visits at 1 and 4 months after surgery.

- **Pain management**: Since pain is a subjective experience, its management will be aligned to each patient's requirement. All participating patients will receive pain control medication, selected in accordance with the WHO Analgesic Ladder (73), as needed. The study does not anticipate a significant difference between the two groups in terms of post-surgical pain.

- **Data security**: Ensuring the security of participant data will be a priority in this study. All electronic data will be stored on secure servers with restricted access, and physical records will be kept in monitored storage areas. Access to sensitive information will be limited to authorized personnel only. This careful approach to data security aims to preserve the privacy and confidentiality of participants throughout the study.

8. STATISTICAL ANALYSIS

The statistical analysis will be carried out by a blinded statistical analyst with the Statistical Package for Social Sciences (SPSS Windows®) version 29.0.1.

For all the results, a p-value less than 0,05 will be considered statistically significant and 95% confidence interval will be defined.

8.1. Descriptive analysis

Variables and covariates will be defined as quantitative or qualitative (*see Variables; Table 5*).

For qualitative variables and covariates, the results will be expressed using **proportions or percentages** and its confidence interval. For quantitative variables and covariates, being either continuous or discrete, **mean ± standard deviation** (symmetric distribution) or **median and interquartile range** (asymmetric distribution) will be used.

8.2. Bivariate analysis

The effect of the type of pre-operative planning method on the qualitative variables, which are the occurrence of persistent enophthalmos and the appearance of post-operative complications, will be assessed by the **Chi-Square test**.

The association between the type of intervention and the quantitative variable, which is the VAS to evaluate satisfaction and understanding by the patient, will be carried out using **Mann-Whitney's U test**.

8.3. Multivariate analysis

Although we anticipate that our groups will be balanced in terms of covariates thanks to the randomization process, if there is suspicion of confounding during the statistical analysis, adjustments will be made to account for potential associations between the independent and dependent variables.

The effect of the type of pre-operative planning method on the qualitative variables, which are the occurrence of persistent enophthalmos and the appearance of post-operative complications, will be assessed by the **logistic regression** adjusted for the covariates.

The association between the type of intervention and the quantitative variable, which is the VAS to evaluate satisfaction and understanding by the patient, will be carried out using the **Poisson regression** adjusted for the covariates.

9. ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted following the ethical principles and guidelines established by the World Medical Association in the **Declaration of Helsinki** for Ethical Principles for Medical Research Involving Human Subjects (1963, last reviewed in October 2013) (74), and in compliance with the **Principles of Biomedical Ethics** proposed by Beauchamp and Childress in 1979.

The principle of **justice**, which consists of the equitable distribution of the benefits of vital well-being while avoiding any discrimination in accessing health resources, will be upheld. All eligible patients, regardless of ethnicity, gender, socioeconomic status, or other factors that might lead to discrimination against a particular group of people, will be invited to participate in the study. The patient's **autonomy** will be respected, as participation in the study will be completely voluntary. Patients will be able to read the Information Form (*Annex 1*) and sign the Informed Consent Form (*Annex 2*) if they want to participate in the clinical trial. It is expected to respect the **non-maleficence** principle, as no malicious intent is being done to the patients participating in the study. Both groups will undergo the same surgical procedure, this being the conventional treatment for orbital floor fractures requiring surgery, and it will be performed in a regulatory hospital by accredited and well-trained health professionals. In case of any adverse effects, the medical team will be highly qualified to solve them. Finally, it is also expected to respect the principle of **beneficence**, which is the moral obligation to act for the benefit of others. All actions will be carried out thinking about what is best for the patient.

This study protocol will be presented to the **Comitè Ètic d'Investigació Clínica (CEIC)** of HUJT for its evaluation and approval, and all their suggestions and requirements will be taken into consideration and added to the protocol. After the CEIC approval, the protocol will be sent to the coordinator of each participant hospital to get their approval and reconfirm their participation. Only after all these entities have approved our study protocol, the clinical trial will start.

This study has also been developed according to the Spanish and European legal precepts of:

- "**Ley 14/2007**, de 3 de julio, de Investigación Biomédica"
- "**Real Decreto 1090/2015**, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos"
- "**Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo**, de 27 de abril de 2016, relative a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la directive 95/46/CE (Reglamento general de protección de datos)"
- "**Ley Orgánica 3/2018**, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales"
- "**Ley 41/2002**, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"

All data collected will only be used for the intended purpose of this study. All investigators will have to declare no conflict of interests, and they will also have to agree to publish all data and results with total transparency, including unfavorable data or events.

10. WORK PLAN AND CHRONOGRAM

10.1. Research team

Personnel involved in this study include:

- **Main Investigator (MI) and Co-Investigator (CI)**: OMF surgeon and second OMF surgeon during surgery. They will be responsible for the entire project, including protocol development, financial management, general coordination, analysis of the results, publication, and dissemination. They will also be involved in recruiting participant patients and obtaining Informed Consent.
- **Clinical Coordinator (CC)**: OMF surgeon. Responsible for ensuring that the protocol is followed as specified, communicating with the research team in case of any doubts, and uploading the information into the REDCap database.
- **3D printing technician**: Responsible for image segmentation and 3D printing of anatomic models for patients in the intervention group.
- **Ophthalmologist**: Conducts the ophthalmological evaluation before and after the surgery.
- **Radiologist**: Performs the pre-operative CT scan.
- **Independent statistician (IS)**: Responsible for the randomization, execution of the statistical analysis, interpretation, and publication of the results. The IS will be blinded to avoid bias.
- **Independent physician (IP)**: Responsible for examining patients during follow-up visits and collecting information in the database. The IP will be different OMF surgeons not involved in planning or performing the surgery. They will be blinded to avoid bias.
- **Data manager (DM)**: Responsible for creating the database to store the collected information and ensuring the security and confidentiality of the data.
- **Collaborators**: Other physicians and nurses involved in the multidisciplinary management of patients undergoing surgical treatment for orbital floor fractures.

10.2. Study stages

The activities developed in this study will be divided in the following stages:

Stage 0: Study design (3 months: November 2023 – January 2024)

- **Activity 1**

Bibliographic research. Systematic literature search on the following topics: orbital floor fractures and in-house 3D printing applications and techniques.

- **Activity 2**

Protocol elaboration including objectives, hypotheses, variables and methodology.

Stage 1: Ethical evaluation (3 months: February 2024 – April 2024)

- **Activity 3**

CEIC evaluation and approval. The protocol will be submitted to the CEIC of HUJT for its revision and approval. Once approved, the protocol will be adapted to the CEIC requirements.

Stage 2: Coordination and training (3 months: May 2024 – July 2024)

- **Activity 4**

Research team meeting. The MI and CI from each participant hospital will select a CC responsible for ensuring protocol adherence as specified and facilitating communication between hospitals. The protocol will be explained, and a work chronogram will be developed, outlining all phases in detail.

- **Activity 5**

Database creation. The DM will establish the database to record information about participant patients. Each participant patient will be assigned with a code number to ensure confidentiality.

- **Activity 6**

Training sessions. All participant collaborators and IP will be trained on what information they must request and how to collect it. Additionally, 3D printing technicians will attend a 10-hour workshop to standardize the printing process. To unify the surgical technique, OMF surgeons from all the participant hospitals will attend a 5-hour workshop.

Stage 3: Field work and data collection (25 months: August 2024 – August 2026)

- **Activity 7**

Recruitment and randomization. A non-probabilistic consecutive sampling method will be followed. Eligible patients meeting the inclusion criteria, not meeting the exclusion criteria, and providing signed Informed Consent Form will be enrolled in the study. The recruitment period is expected to last 20 months. Participant patients will be randomly assigned to the control or the intervention group.

- **Activity 8**

Intervention and discharge. The pre-operative planning method will be performed for each patient based on their assigned group, with or without the 3D printing model. Before surgery, the patient understanding and satisfaction will be assessed with the VAS by an IP, and the results will be recorded in the patients' clinical chart. Following surgery, all patients will undergo a two-day hospitalization period before discharge.

- **Activity 9**

Follow-up sessions conducted by an IP. Follow-up sessions are scheduled at 2 weeks, 1 month and 4 months after surgery. During these sessions, the following variables will be assessed: the occurrence of enophthalmos and the occurrence of post-operative complications, including persistent diplopia, restricted EOM motility, and infraorbital nerve dysfunction.

- **Activity 10**

Data collection. An IP will systematically collect and record all the information, including the pre-operative VAS assessment and data from each follow-up visit, in the patients' clinical chart. The CC will then compile and transfer this information to the study REDCap database.

Stage 4: Data analysis and interpretation (3 months: September 2026 – November 2026)

- **Activity 11**

Statistical analysis. The IS will conduct the statistical analysis using the data collected in the REDCap database during the third stage of the study. The results will be sent to the MI and CI of each participant hospital, and the CC.

- **Activity 12**

Discussion and conclusions. The interpretation of the statistical analysis will be carried out by the MI and CI of each participant hospital, along with the CC. Subsequently, the discussion and conclusions will be elaborated.

Stage 5: Data publication and dissemination (4 months: December 2026 – March 2027)

- **Activity 13**

Article writing, revision and publication. The MI and CI of each participant hospital, in collaboration with the CC, will write a journal article providing a detailed explanation of the entire process. The article will undergo editing by English language editors before being published.

- **Activity 14**

Dissemination of the research findings will be actively pursued through scientific outreach. The results will be presented or sent to conferences organized by "Societat Catalano-Balear de Cirurgia Maxil·lofacial i Oral" (SCBCMO), "Sociedad Española de Cirugía Oral y Maxilofacial y de Cabeza y Cuello" (SECOM CyC), "British Association of Oral and Maxillofacial Surgeons" (BAOMS), and "European Association for Cranio-Maxillo-Facial Surgery" (EACMFS).

The study chronogram can be seen in *Table 7*.

Table 7. Study chronogram

STAGES AND ACTIVITIES	YEARS																																								
	2023		2024												2025												2026												2027		
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M
STAGE 0: STUDY DESIGN																																									
Activity 1: Bibliographic research	X																																								
Activity 2: Protocol elaboration	X	X	X																																						
STAGE 1: ETHICAL EVALUATION																																									
Activity 3: CEIC evaluation and approval				X	X	X																																			
STAGE 2: COORDINATION AND TRAINING																																									
Activity 4: Research team meeting							X																																		
Activity 5: Database creation							X																																		
Activity 6: Formation sessions							X	X	X																																
STAGE 3: FIELD WORK AND DATA COLLECTION																																									
Activity 7: Recruitment and randomization										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												
Activity 8: Intervention and discharge										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												
Activity 9: Follow-up sessions										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Activity 10: Data collection										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
STAGE 4: DATA ANALYSIS AND INTERPRETATION																																									
Activity 11: Statistical analysis																																			X	X					
Activity 12: Discussion and conclusions																																					X				
STAGE 5: DATA PUBLICATION AND DISSEMINATION																																									
Activity 13: Writing, revision and publication																																						X	X	X	
Activity 14: Dissemination																																									X

11. BUDGET

11.1. Personnel expenses

The personnel costs for the research team, including the MI, CI, CC, IP, radiologists, ophthalmologists, and collaborators involved in the multidisciplinary management of patients undergoing surgical treatment for orbital floor fractures, will not suppose any additional cost, as they are salaried by the participant hospitals.

A 3D printing technician will be employed for each participant hospital, with a compensation of 40€/h, working approximately 320 hours each. The total cost for this role will amount to 76.800€.

Additionally, an IS and a DM will be hired, with a compensation of 40€/hour, working approximately 150 hours each. The total cost for these positions will be 12.000€.

11.2. Training expenses

Three training sessions are scheduled for the study:

- A 5-hour workshop for all OMF surgeons in each hospital to unify the surgical technique.
- A 10-hour workshop for all participating 3D printing technicians to standardize the 3D printing process.
- A 5-hour training session for the IP on information requirements and outcomes assessment (VAS, Hertel exophthalmometer, post-operative complications).

11.3. Insurance

No insurance policy will have to be considered in this clinical trial, given its classification as low risk.

11.4. Execution expenses

For the intervention, each participant hospital will utilize a Creality Ender-3 V2 3D printer**.** With six participant hospitals, and the price of each printer being 279€, the total cost will be 1.674€.

The material for printing the 3D anatomical models will be biodegradable and recycled PLA. For all participant hospitals, 33 PLA filament reels will be purchased, and the cost of each reel is 8,50€. The total cost will be 280,50€.

Additionally, a total of 132 Information Forms, 132 Informed Consent Forms, and 132 VAS copies will be printed.

Surgical material expenses and pre-operative CT scans will not be included in the budget, as they are already available in the hospital, and pre-operative CT scans are considered the conventional imaging technique for orbital floor fractures.

11.5. Travel and coordination expenses

The research team meetings will be conducted online. Travel expenses for training sessions will be covered with a budget of 300€.

11.6. Publication expenses

Once the article is written, it will undergo editing by English language editors before being published (500€). Subsequently, it will be published as an Open Access article (1.800€). The total cost will amount to 2.300€.

11.7. Dissemination expenses

To disseminate the study results, the MI will attend national and European congresses on OMF surgery.

Table 8. Budget details of the study

ITEM	UNIT COST	UNITS	SUBTOTAL
PERSONNEL			
Six 3D printing technicians	40€/h	320h each	76.800€
IS	40€/h	150h	6.000€
DM	40€/h	150h	6.000€
TRAINING			
OMF surgeons' workshop	50€/h	5h in each hospital	1.500€
3D printing workshop	50€/h	10h	500€
IP training	50€/h	5h	250€
EXECUTION EXPENSES			
Creality Ender-3 V2	279€	6	1.674€
PLA	8,50€	33	280,50€
Photocopies	0,05€	396	19,80€
TRAVEL AND COORDINATION			
Training professionals			300€
PUBLISHING			
English edition			500€
Open access publication			1.800€
DISSEMINATION			
SCBCMO (Catalan congress)	1 inscription fee		150€
	1 travel and accommodation		250€
SECOM CyC (Spanish congress)	1 inscription fee		200€
	1 travel and accommodation		350€
EACMFS (European congress)	1 inscription fee		400€
	1 travel and accommodation		700€
INSURANCE POLICY			
Liability insurance	-	-	0€
TOTAL: 97.674,30€			

12. STUDY LIMITATIONS

During the design process of this clinical trial protocol, certain limitations have been identified and will be addressed and considered:

- The sampling employed in this study is a **consecutive non-probabilistic recruitment method**, which may introduce **selection bias** impacting the external validity by not representing the entire population adequately. However, to mitigate this potential bias, all participants will undergo randomization into one of the two groups. Additionally, a multivariate analysis adjusted for covariates will be conducted.

- This clinical trial is **open-label** due to the impracticality of masking patients and OMF surgeons, potentially leading to **detection bias**. To mitigate this, participant patients will be assigned numeric codes for anonymity. Outcomes will be assessed by an independent physician (IP), patients will be instructed not to disclose their pre-operative planning type, and statistical analysis will be conducted by an independent statistician (IS).

- Given the **prospective** nature of the study, there is a **risk of potential withdrawals** during the follow-up period. To account for this risk, a 10% drop-out rate has been considered into the sample size determination, and the overall sample size has been increased accordingly. Additionally, proactive measures will be taken, including telephone calls to absent participants on their follow-up visits. If direct contact cannot be established, an attempt will be made to reach a family member using the contact information registered in the patients' clinical chart.

- Considering the **multicentric** nature of the study, there is a possibility of **variability** among different physicians in terms of pre-operative planning and outcome assessment. Moreover, it is important to note that the Hertel exophthalmometer is operator dependent. To minimize this potential variability, training sessions will be conducted to standardize procedures and ensure

uniformity in approaches. Furthermore, before starting the clinical trial, the research team will meet to thoroughly explain the protocol, and the clinical coordinator will be able to address any doubts throughout the entire duration of the trial.

13. CLINICAL AND HEALTHCARE IMPACT

Orbital floor fractures are one of the most frequent types of fractures among young adults in the OMF field, and their anatomy poses a challenge for any surgeon. With a thickness of 2 mm and a gradual slope from the medial to the lateral side, accurate reconstruction is imperative to restore normal anatomy and prevent enophthalmos.

To reduce the occurrence of persistent enophthalmos, as well as other post-operative complications such as persistent diplopia, infraorbital nerve dysfunction, and restricted EOM motility, this study proposes the integration of personalized medicine, throughout in-house 3D printing, in the pre-operative planning of orbital floor fractures surgeries. This methodology involves the 3D printing of an individualized anatomical model of the patient's fracture and its mirroring. This model allows OMF surgeons to thoroughly analyse the patient's specific anatomy and plan the surgical approach accordingly. Furthermore, the titanium mesh plate can be precisely pre-bent into the anatomical model, ensuring a perfect fit to the individualized anatomy of the patient.

Additionally, these 3D printed anatomical models may serve as valuable tools for pre-surgical communication with patients, enhancing their understanding of the pathology and potentially contributing to increase their satisfaction and engagement.

In conclusion, this study opens the door to a new pre-operative planning method, utilizing the innovative path of 3D printing and personalized medicine, with the potential to achieve superior outcomes in orbital floor fractures.

14. FEASIBILITY

This study is considered feasible for various reasons.

Firstly, the well-prepared research team that designed the clinical trial is prepared to conduct it effectively. Despite being a multicentric study, regular and efficient communication among all researchers is anticipated. With a target of enrolling 132 patients over 20 months, the timeframe is deemed reasonable from a logistical standpoint.

Moreover, all surgical interventions will be carried out by highly trained healthcare professionals. To ensure procedural consistency, preparatory workshops are planned. The work plan has been meticulously scheduled, allowing for an adequate timeline to execute all activities effectively.

Lastly, it its relevant to mention that our protocol will undergo evaluation and approval by the CEIC before initiation, adhering to ethical considerations and ensuring complete transparency. Additionally, the results, whether favourable or not, will be published and disseminated to contribute to the progress of medicine.

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16. ANNEXES

16.1. Annex 1: Information Form

FULL D'INFORMACIÓ PER AL PACIENT SOBRE LA PARTICIPACIÓ EN L'ESTUDI

Nom de l'estudi: "Ús de models anatòmics impresos en 3D en el mateix hospital per a la planificació preoperatòria en pacients sotmesos a cirurgia de fractures aïllades de terra d'òrbita". **Hospital**: **Investigador/a principal**:

Benvolgut/da,

Ens dirigim a vostè per a proposar-li participar en un estudi d'investigació dut a terme al servei de Cirurgia Oral i Maxil·lofacial de l'hospital ..... Aquest estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica de l'hospital, d'acord amb la legislació vigent, "**Ley 14/2007, de 3 de julio, de Investigación Biomédica**" i amb respecte als principis enunciats en la declaració d'Hèlsinki i a les guies de bona pràctica clínica.

La nostra intenció és que vostè entengui el motiu pel qual es realitza aquest estudi i què implica formar-ne part, per tal que pugui decidir voluntàriament si desitja participar-hi. Per això, li preguem que es prengui el temps necessari per llegir detingudament i comprendre aquest resum informatiu sobre el nostre estudi. No cal que decideixi avui la seva participació i, en cas que sorgeixi qualsevol dubte, el nostre equip estarà pendent i el respondrà, posant a la seva disposició tota la informació necessària.

DESCRIPCIÓ GENERAL DE L'ESTUDI

<u>Per què és necessari aquest estudi i quin és el seu objectiu?</u>

Aquest estudi té com a principal objectiu investigar i comparar dues tècniques de planificació pre-quirúrgica, que es duen a terme per part de l'equip de Cirurgia Oral i Maxil·lofacial, per tal de millorar els resultats i disminuir les complicacions post-quirúrgiques en pacients sotmesos a cirurgia reparadora de fractures de terra d'òrbita.

Les fractures de terra d'òrbita són freqüents en el camp de la Cirurgia Oral i Maxil·lofacial i solen afectar a adults joves. Aquestes fractures tenen una repercussió tant estètica com oftalmològica. Estèticament, poden provocar asimetries facials causades per la diferent posició dels ulls i, aquesta diferència entre els dos ulls, pot acabar donant afectació visual com la diplopia (visió doble). A més, es pot veure afectat el nervi infraorbitari, que passa just per sota del terra de l'òrbita, provocant una disminució de la sensibilitat a zones de la cara com la vora inferior de la parpella, la galta, el llavi superior i la geniva. Una altra de les possibles conseqüències de les fractures de terra d'òrbita és la restricció en la motilitat de l'ull per l'afectació dels músculs extra-oculars, que s'encarreguen de moure l'ull per fer totes les posicions de la mirada.

Totes aquestes repercussions de les fractures de terra d'òrbita es poden tractar amb la cirurgia reparadora del defecte però, aproximadament un 30% dels pacients, segueixen tenint seqüeles després de la cirurgia manifestades com enoftalmos (enfonsament de l'ull respecte l'ull sa) o visió doble, entre d'altres.

Per tal de disminuir la ocurrència d'aquestes seqüeles post-quirúrgiques, el nostre estudi planteja la integració de la impressió 3D en la planificació de les cirurgies. Amb una impressora 3D a l'hospital, s'imprimirà un model anatòmic de la fractura a partir de la Tomografia Axial Computeritzada (TAC) feta quan el/la pacient arriba a l'hospital. Amb aquest model anatòmic, l'equip de cirurgians podran estudiar el tipus de fractura, plantejar quin és el millor procediment a seguir i, moldejar l'implant de titani que posteriorment s'implantarà al/la pacient.

METODOLOGIA I INTERVENCIÓ

<u>En què consisteix la meva participació en l'estudi?</u>

L'estudi s'oferirà a un total de 132 pacients, majors de 18 anys, que s'hagin de sotmetre a una cirurgia reparadora d'una fractura aïllada de terra d'òrbita. Una vegada el/la pacient hagi acceptat participar en l'estudi, li serà assignat un codi numèric i serà aleatoritzat en un dels dos grups:

- Grup A: La planificació pre-quirúrgica inclourà la impressió del model 3D.
- Grup B: La planificació pre-quirúrgica serà la convencional.

A tots els/les pacients se'ls hi farà la mateixa prova d'imatge (TAC) i, prèviament a la cirurgia, se'ls hi explicarà el procediment i se'ls hi passarà una enquesta ràpida per valorar la seva comprensió sobre la fractura i el procediment, i la seva satisfacció respecte la informació rebuda.

Finalment, tots els/les pacients seran intervinguts quirúrgicament de la mateixa manera, és a dir, el tipus de planificació pre-quirúrgica no canviarà el tipus d'intervenció quirúrgica. Posteriorment, una vegada els/les pacients rebin l'alta mèdica, es farà un seguiment a consultes externes a les 2 setmanes, 1 mes i 4 mesos després de la cirurgia.

BENEFICIS I RISCS DE L'ESTUDI

<u>Quins beneficis obtindré de la meva participació en l'estudi?</u>

Amb la seva participació en l'estudi ajudarà a ampliar el coneixement mèdic sobre els beneficis de la integració de la medicina personalitzada i la impressió 3D en la planificació quirúrgica de les fractures en l'àmbit de la Cirurgia Oral i Maxil·lofacial, concretament en les fractures de terra d'òrbita.

<u>Quins riscs assumeixo si participo en l'estudi?</u>

No es preveuen riscs addicionals en la participació de l'estudi, ja que tant les proves d'imatge prèvies a la cirurgia com el tipus d'intervenció quirúrgica són les utilitzades en la pràctica clínica habitual per les fractures de terra d'òrbita.

CONFIDENCIALITAT

Com s'assegurarà la confidencialitat de les meves dades personals?

La confidencialitat estarà protegida i la informació recollida en aquest estudi serà tractada segons la "**Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales**" i el "**Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativa a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos**". Les dades recollides es tractaran de forma confidencial, sense accés per part de tercers i només seran utilitzades amb finalitats d'investigació. La recollida de dades no inclourà cap tipus d'informació que permeti identificar al/la pacient, com nom i cognoms, DNI, número d'història clínica ni altra informació personal. Les dades aniran vinculades a un codi numèric.

DIFUSIÓ DELS RESULTATS

Que se'n farà dels resultats obtinguts en l'estudi?

Un cop hagi finalitzat l'estudi, s'extrauran els resultats i s'elaboraran les conclusions. Es preveu la publicació dels resultats a revistes científiques, tant si el resultat és positiu com si és negatiu. Tot aquest procés es farà sempre respectant l'anonimat dels participants.

COMPENSACIÓ ECONÒMICA

Tindré alguna compensació econòmica si participo en l'estudi?

Els investigadors/es que participen en l'estudi no reben cap tipus de benefici econòmic. La participació a l'estudi és voluntària i, per tant, no serà remunerada.

CONTACTE

En cas de qualsevol dubte abans, durant o després de la realització d'aquest estudi, podrà posar-se en contacte sempre que ho necessiti amb: .....

Moltes gràcies per la seva col·laboració.

16.2. Annex 2: Informed Consent Form

DOCUMENT DE CONSENTIMENT INFORMAT DEL PACIENT

Jo, ……., amb document d'identificació personal (DNI/NIE) ……., declaro que:

- He llegit i entès tota la informació que apareix a la fulla d'informació per al pacient.
- Estic satisfet/a amb la quantitat d'informació que se m'ha proporcionat.
- He pogut exposar els dubtes que m'hagin sorgit, i me'ls han resolt adequadament.
- Entenc els potencials riscs i beneficis derivats de participar en aquest estudi.
- No he ocultat informació essencial sobre el meu cas, els meus hàbits o règim de vida, que poguessin ser rellevants pel personal sanitari que m'atén.
- Comprenc que la meva participació és voluntària i no remunerada.
- Comprenc que les meves dades personals i proves seran confidencials.

Sé, per altra banda, que m'intervindrà el facultatiu que, dins de les circumstàncies de l'equip mèdic en el dia de la meva intervenció, sigui el més adequat per al meu cas. Per tot això, **DONO EL MEU CONSENTIMENT PER A PARTICIPAR EN L'ESTUDI**, així com per què els investigadors del projecte puguin posar-se en contacte amb mi en un futur si es considera oportú. En el cas que, durant la intervenció, el cirurgià/na trobi aspectes de la meva malaltia que li exigeixin o li aconsellin modificar el procediment inicialment projectat, podrà fer-ho de la manera que millor convingui a la meva salut.

A més, comprenc que tot i haver firmat el document de consentiment informat, puc revocar-lo en qualsevol moment i que això no suposarà un perjudici en el meu tractament ni en la meva assistència sanitària.

Signatura del/la pacient **Signatura de l'investigador/a**

- ○ Accepto
- ○ No accepto

Lloc i data: ....., ... de ..... de l'any .....

DOCUMENT DE REVOCACIÓ DEL CONSENTIMENT INFORMAT DEL PACIENT

Jo, ……., amb document d'identificació personal (DNI/NIE) ……., revoco el consentiment prèviament signat per a la participació en l'assaig clínic: "Ús de models anatòmics impresos en 3D en el mateix hospital per a la planificació preoperatòria en pacients sotmesos a cirurgia de fractures aïllades de terra d'òrbita".

Signatura del/la pacient **Signatura de l'investigador/a**

Lloc i data: ....., ... de ..... de l'any .....

16.3. Annex 3: Visual Analogue Scale (VAS)

Patient understanding and satisfaction with the information received about their treatment process