EXPLORING THE DIVERGENCE IN CLINICAL TRIAL DESIGN, APPROVAL PATHWAYS AND CLINICAL OUTCOMES IN TELEMEDICINE: A CASE STUDY OF A REMOTE VIDEO-OTOSCOPIC IMAGING DEVICE IN TELEHEALTH APPLICATIONS

Ph.D. Thesis

Ádám Pannonhalmi Pharm.D.

Doctoral School of Clinical Medicine

University of Szeged

Supervisor:

Prof. Dr. Lajos Kemény

Department of Dermatology and Allergology

University of Szeged

Szeged, Hungary

2025

TABLE OF CONTENTS

1. Introduction 1
1.1. Regulation of clinical trials for drugs in the European Union 2
1.2. Clinical trials for medical devices in the European Union 5
1.3. Telemedicine and e-health in otorhinolaryngological settings 8
1.4. Translation of telemedical solutions into clinical application 10
2. Aims 12
3. Methodology 13
3.1. Analysis and comparison of clinical trial routes based on product category 13
3.2. Evaluation of the performed telemedical clinical trial 13
3.2.1. Applied telemedicine device and software 13
3.2.2. Participants of the study 14
3.2.3. Study protocol 15
3.2.4. Data analysis 17
4. Results 18
4.1. Comparative analysis of the EU clinical trials based on product category 18
4.2. Evaluation of the clinical trial performed on the oto-videoscopic remote diagnostic system 23
4.2.1. Demographic and basic characteristics 23
4.2.2. Number of matches in the diagnoses together 23
4.2.3. Number of matches in the diagnoses individually 25
4.2.4. Number of matches in the therapies individually 26
4.2.5. Number of matches in the diagnoses in the case of different therapies 28
4.2.6. Matching by optional diagnosis 30
4.2.7. Overlapping in diagnoses and therapies 34
5. Discussions 36
5.1. Comparison and analysis of clinical trials based on product category 36
5.2. Evaluation of the performance of the oto-videoscopic telemedical device 38
5.3. Application of telemedicine in otorhinolaryngology 39
6. Conclusions 41
7. Acknowledgements 43
8. References 44

LIST OF PUBLICATIONS

I. **Pannonhalmi Á**, Posta B, Perényi Á, Rovó L, Bende B, Katona G, Csóka I, Kemény L, Szakács L. Clinical validation of a video-otoscopy-based medical device for the remote diagnosis of ear complaints. Sensors 2025; 25(3): 758. (Q1, IF: 3.5)

II. **Pannonhalmi Á**, Sipos B, Kurucz RI, Katona G, Kemény L, Csóka I. Advancing regulatory oversight of medical device trials to align with clinical drug standards in the European Union. Pharmaceuticals 2025; 18(6): 876. (Q1, IF: 4.8)

III. Bende B, **Pannonhalmi Á**, Németh A, Miglinci L, Kemény L. A transzlációs medicina aktuális kérdései a mai magyar bőrgyógyászatban. Beavatkozással járó, vizsgálói kezdeményezésű klinikai vizsgálatok kivitelezésének jó gyakorlata. BVSZ 2019; 95(6): 267.

IV. **Pannonhalmi Á**, Bende B, Szakács L. Clinical validation of video-otoscopy based medical device for remote diagnosis of ear complains. V. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science. January 18-20, 2023 - Szeged, Hungary. Book of Abstracts 2023; FP-07: 62.

V. **Pannonhalmi Á**, Vass A, Bende B, Csóka I, Kemény L. Patient safety issues in telemedicine application development in case of peripheral arterial disease. 4th International Conference on Pharmaceutical and Medical Sciences. September 16-18, 2022 - Martin, Kraków, Szeged. Conference Book 2022; 90-91.

LIST OF ABBREVIATIONS

ADR	adverse drug reaction
CER	Clinical Evaluation Report
CIP	Clinical Investigation Plan
CPAP	continuous positive airway pressure
CTA	clinical trial application
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EMA	European Medicines Agency
ENT	Ear-nose-throat
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
ICD	International Statistical Classification of Diseases and Related Health Problems
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostics Regulation
MDCG	Medical Device Coordination Group
MDD	Medical Device Directive
MDR	Medical Device Regulation
PMCF	post-market clinical follow-up
QMS	quality management system
RCT	randomized controlled trial
SMEs	small-and medium-sized enterprises
UDI	Unique Device Identification

1. Introduction

The global market for drugs and medical devices is a rapidly evolving sector of the pharmaceutical industry, directly affecting daily interpretation and utilization of innovations in healthcare, academic research, and economic development [1]. Clinical trials are a cornerstone of evidence-based medicine, which forms the basis for approval and integration of novel therapeutic interventions into routine clinical practice. Over the past decades, the methodological landscape of clinical trials has evolved remarkably, especially in the domains of pharmaceuticals and medical devices [2,3]. Whilst clinical trials for drug development are guided by well-established, straightforward regulatory frameworks and standardized protocols, medical devices pose a more challenging area due to the variability in this product category, which is shaped by the inherent complexity and variability of device design, human factors, and user interactions [4,5].

Telemedicine is a rapidly growing field in daily clinical practice that leverages digital communication technologies to deliver healthcare remotely, introducing unprecedented flexibility in patient-provider interactions. The main advantage of telemedicine stems from its ability to merge healthcare services with information technology through distinctive user interfaces and remote diagnostic capabilities, and asynchronous data exchange methods [6]. The transition to telemedicine introduces new variables, which include connectivity issues and device usability problems, and patient digital literacy challenges that do not exist in conventional face-to-face healthcare delivery [6]. The distinctive features of telemedical trials need to be recognized as separate from standard clinical trials. Telemedical interventions need distinct outcome measures and decentralized trial designs and must address confounders that stem from technology use. The evolving regulatory, ethical, and logistical frameworks for telemedicine require trial designs that properly address its unique operational and clinical characteristics. Telemedicine is particularly important in otorhinolaryngology due to the high prevalence of conditions that can be initially assessed through visual and auditory examination, such as ear infections. It enables timely access to specialist evaluation, particularly in remote areas where in-person otolaryngology services are limited [6,7].

Understanding how clinical trials for various product categories and how telemedical devices differ from traditional drug trials, especially in terms of design, regulation, and implementation. Evaluating a novel telemedical device contributes to the advancement of accessible, high-quality ear care and supports the broader integration of telemedicine in routine practice.

1.1. Regulation of clinical trials for drugs in the European Union

In the EU, Clinical Trials Regulation (CTR) No. 536/2014 is implemented to govern the conduct of clinical trials involving medicinal products for human use [8]. It was adopted on the 16th of April 2014 and made applicable on the 31st of January 2022. Before that, the Clinical Trials Directive (CTD) 2001/20/EC was utilized [9]. This particular regulation aims to harmonize the assessment and supervision of all clinical trials executed in the European Union (EU) member states. It not only ensures the quality of clinical trials but also promotes innovation in medical research with high safety and transparency standards. Elements and mandatory requirements of Good Clinical Practice (GCP, ICH E6) are also included in Regulation No. 536/2014 [10]. There were multiple discrepancies in the implementation of clinical trials across each member state, leading to heavy administrative burdens and inefficient authorization processes [11]. The regulation aims to create a single, streamlined system to apply for every one of the Clinical Trial Applications (CTA), to gain public access to clinical data, while ensuring that all the participant's safety is met to the highest standards. A comparison of the Clinical Trials Regulation (CTR) No. 536/2014 and CTD 2001/20/EC can be found in Table 1.

Table 1. Comparison of CTD 2001/20/EC and the currently effective CTR No. 536/2014 [8,9]. Abbreviation used in this table: CTIS – Clinical Trials Information System.

Feature	Directive 2001/20/EC	Regulation No. 536/2014
Ethics Committee role	national discretion	in ordinance with all member states
Application submission	separately to each member state	single application via CTIS
Assessment timeline	varying between member states	harmonized deadlines
Risk-based supervision	uniform requirements	based on risk level
Transparency	Limited public access	mandatory public access
Safety reporting	varying formats between member states	standardized

The key feature of CTR is the implementation of a single clinical trials application and authorization process applied to each member state on a centralized online platform, namely the Clinical Trials Information System (CTIS). It is designed to streamline the submission process, the assessment, and the supervision by regulatory agents of clinical trials across the EU [12]. It is accessible to all stakeholders to ensure that all steps are transparent and efficient, and all data can be unified to the regulatory bodies, the sponsors and the public. The sponsors

submit a single application form via CTIS for clinical trials conducted in multiple member states to avoid the duplication of data. The application can be divided into two main parts. The first part includes the coverage of scientific and clinical aspects, the trial design, applied methodology, what safety measures are applied, and the risk assessment process and evaluation strategy for the resulting data [13]. This process ensures that the study meets high scientific and ethical standards. The second part includes the national-specific considerations based on patient recruitment strategies, specific ethical review processes, and consent procedures to meet the individual member state's requirements. After all data has been provided in the submission, a harmonized decision-making process follows, involving coordinated assessments [14,15].

After submission, an initial validation phase is implemented, during which regulatory authorities verify and determine the completeness and compliance with the required standard. Following validation, a review process begins, both scientifically and ethically, involving regulatory agencies, relevant public health authorities, and, last but not least, ethics committees [10, 16, 17. This is a strict process to ensure that the trial is acceptable in the early phases based on the possible risk factors associated. If only one member state is involved in the trial, then the reporting member state is the leader of the evaluation, and they provide the initial decision. If other members are involved, then all evaluations and decisions must be collected before the final authorization. If approved, the sponsors and the regulatory bodies both continue to monitor and fill in data on the progress through CTIS [16]. These data include regular updates on trial progress and any protocol modifications and amendments. Reporting adverse and safety-concerning events is mandatory; if missed, the clinical trial could be penalized or completely shut down [17]. Interim results are also of paramount importance to regulatory bodies to ensure data integrity and compliance with the priorly approved scientific and ethical standards [18].

Clinical trials for medicinal products must undergo all phases; however, they can be categorized based on the level of risk posed to participants. Low-intervention trials involve investigational drugs that already possess approval for use, and where the safety profile is established, whilst high-risk trials include novel drug combinations, drugs, or new applications of existing data, where the safety data is limited [19,20]. Risk assessment frameworks must be implemented in a structured manner to ensure that the high-risk trials receive greater scrutiny and regulatory oversight [21]. Remote monitoring or data review is usually used for low-risk trials, but it does not substitute for the on-site standby by professionals [22]. The utilization of telemedicine as wearable technology allows remote monitoring and real-time tracking of patient vitals. Additionally, the constant data flow allows better data management [23,24].

There are multiple benefits to the implementation of Regulation 536/2014. For sponsors and researchers, it is claimed that it provides a simplified submission process, lower costs, and a faster time-to-market [14]. The CTIS aims to streamline processes under regulation, but early experiences show mixed results. The European Organization for Research and Treatment of Cancer (EORTC) conducted a study that revealed that regulatory comment response times averaged 27.5 days beyond the 12-day limit established by the regulation, thus indicating a need to enhance internal processes for new timeline compliance [25]. Three multinational European clinical studies showed that approval timelines remain unacceptable despite some improvements because of conflicting application requirements and technical issues within CTIS [26]. The regulation's objectives are clear, but there is no concrete evidence to support reduced time-to-market and costs [27]. A general structure of the authorization process of clinical trials for medicinal products can be seen in Figure 1.

Figure 1. Schematics of the steps of clinical trials for medicinal products according to CTR No. 536/2014. Abbreviations used: CTIS – Clinical Trials Information System.

1.2. Clinical trials for medical devices in the European Union

The Medical Device Regulation (MDR) changed the regulatory framework compared with the prior Medical Device Directive (MDD) [28,29]. The complete integration from May of 2021 brought significant challenges for medical device manufacturers, developers, and the (inter)national regulators. The MDR system has led to the reclassification of numerous devices from Class I or IIa to Class IIb or III, which demands more complex clinical investigations and post-market clinical follow-up (PMCF) [30]. Under MDR, all active implantable devices and their accessories are now classified as Class III, the highest risk category, necessitating rigorous clinical evaluations and conformity assessments [31]. Devices composed of substances intended to be introduced into the human body via a body orifice or applied to the skin have been up-classified [32]. For instance, certain nasal sprays and wound protection creams, previously Class I, may now fall under Class IIa or IIb, depending on their absorption and systemic effects. The transition has caused longer trial periods because of enhanced sample size needs and more demanding endpoints, and longer follow-up durations. The new requirements for clinical evidence and technical documentation have forced small- and medium-sized enterprises (SMEs) and manufacturers of all sizes to dedicate major financial and human resources [33]. The process has proven especially challenging for existing MDD devices because they need new conformity assessments, together with updated clinical data, to stay in the market. The European Commission's Medical Device Coordination Group (MDCG) and MedTech Europe have documented product recertification delays and device withdrawals, and notified body capacity shortages, which demonstrate MDR implementation's extensive system-wide effects [34,35].

The MDCG oversees all aspects of medical device development up to market placement as an expert advisory body established under the MDR and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) [36]. As a basic principle, the manufacture of medical devices must fall under the implementation of the Quality Management System (QMS) by Article 10(9) of the MDR [37]. Regulatory compliance is of highest importance, with detailed management tools on resource and personnel management, supplier and subcontractor control, monitoring of product quality and performance, and finally, the risk management implied in the manufacturing stage. According to MDCG 2021-24, risk management is an integral component of QMS and must be implemented according to ISO 14971 [38,39]. As an additional risk of the 21st century, software and cybersecurity threats must also be addressed, guided by MDCG 2019-16 and MDCG 2022-5, to validate the software according to its intended purposes and

ensure cybersecurity measures are embedded from design to decommissioning [40,41]. The EU has also implemented stringent regulations for medical devices to ensure their performance, safety, and efficacy. The EU MDR 2017/745 has replaced the prior MDD 93/42/EEC. The main differences can be found in Table 2.

Table 2. Comparison of MDR 2017/745 and the prior MDD 93/42/EEC [28,29]. Abbreviations used: MDR—Medical Device Regulation; MDD—Medical Device Directive; UDI – Unique Device Identification.

Aspect	MDR 2017/745	MDD 93/42/EEC
Legal framework	binding regulation	directive
Scope	covers a broader range of services	gaps regarding certain products
Classification of devices	stringent classification rules	less strict classification rules
Clinical evidence requirements	stronger requirements	less stringent requirements
Post-market surveillance	enhanced requirements	basic requirements
Safety reporting	varying formats between member states	standardized
UDI	mandatory	non-mandatory
Notified bodies oversight	stronger role and increased scrutiny	less oversight and scrutiny
Database	fully integrated database with public access	limited database and availability
Manufacturer responsibilities	greater and stricter	fewer responsibilities

Regarding the regulations of clinical trials under the MDR, Articles No. 62–82 address their scientific, ethical, and authorization aspects. Article 62 outlines the fundamental requirements for conducting clinical trials. It is mandatory to comply with GCP, just like in medicinal products, to ensure safety and patient rights. Manufacturers may justify the necessity of clinical investigation, but only if there is sufficient data from previous products or trials. The study design must be robust, and a clear methodology and protocol must also be set up, especially for high-risk classified devices. The same principles apply regarding ethical considerations for medicinal products. Article 63 describes the necessity for informed consent, which is especially important for vulnerable populations, such as minors, and pregnant or breastfeeding women [42]. The same rules apply; if minors are involved in the trial process, then their assent must also be obtained, in addition to parental consent. The mentioned

vulnerable populations and their specifications are mentioned in Articles 65 to 67. The extension of the obtainment of an informed consent form is addressed in Article 64, where the principles of clinical investigations on incapacitated subjects are also considered. The rest of the articles describe the means to comply with the supervisory regulatory authorities. Ethical approval is also based on multiple factors, including the scientific evaluation of the proposed trial, its risk–benefit analysis, the qualifications of investigators, and finally, the assessment of the informed consent procedures and documentation. The average approval time lies between 60 and 90 days if all safety and regulatory requirements are met, followed by registration in the EUDAMED database to ensure publicly accessible data [43]. The results of the trial must be collected into a Clinical Evaluation Report (CER), which is a critical document according to the MDR. The structure of the report must be made in alignment with MDR Annex XIV Part A to ensure a systematic approach to clinical evaluation. The CER must include the clinical background of the medical device investigated from design characteristics, intended use, and clinical applications. The statistical analysis must also be performed in a manner that it can be comparable with prior devices (if they exist). As it is a living document, all new data from post-market surveillance and adverse effects must be added to the document [44].

Similarly to medical devices, recent changes have been implemented in combined drug–device products [45]. According to the European Medicines Agency (EMA) guideline on quality documentation for medicinal products when used with a medical device, three main groups can be detected according to the position and utilization of medical devices in the administration or preparation of drugs (integral drug–device combination). Medical devices, or some of them, can be an integral part of the product without the possibility of reusing, such as prefilled syringes. Co-packaged products (medicine with a co-packaged device) are another type of these products, and the ones called referenced devices also fall under this guideline [46]. From the manufacturing side, both Good Manufacturing Practice (GMP) and the ISO 13485 must be followed [47,48]. A schematic of the authorization of clinical trials for medical devices can be found in Figure 2.

Figure 2. Schematics on the clinical trial authorization process of medical devices according to MDR 201/745. Abbreviations used: CIP—clinical investigation plan; CER—clinical evaluation report.

1.3. Telemedicine and e-health in otorhinolaryngological settings

The development of computer science technology and its innovations enables healthcare facilities to integrate their advantages into everyday clinical practice [49,50]. The medical specialty of otorhinolaryngology or ENT (ear, nose, and throat) underwent a fundamental change because of telemedicine and e-health and telehealth technology advancements. The digital tools available today have extended research possibilities as well as educational and clinical operations and patient care practices [51]. The essential function of these tools lies in improving patient adherence because they overcome restrictions found in conventional healthcare systems and the current COVID-19 pandemic [52,53]. E-health in otorhinolaryngology represents a fundamental shift beyond technological advancement because it transforms medical care delivery methods. ENT healthcare services primarily rely on physical patient assessments combined with ear tests and surgical interventions for their operations. Digital health tool advancements have expanded the diagnostic capabilities for ENT patients while supporting their home-based self-management [54,55].

Telehealth services have created a connection between patients and providers through virtual consultations and remote diagnostics, and asynchronous communication options. Patients now choose e-health technologies because they want convenient care with quick access and individualized attention, which drives fast adoption rates. Telehealth enables patients to take charge of their healthcare while providing them with better access to specialized care without the limitations of travel and clinic hours [56]. The growing worldwide digital literacy creates extensive potential for e-health applications in otorhinolaryngology [54].

E-health provides various advantages for ENT care delivery which produces substantial effects on clinical practice and healthcare delivery and patient outcomes. The most important advantage of e-health systems is their ability to enhance the accessibility of ENT care. The shortage of otolaryngologists exists in numerous regions which include both rural and underserved areas. Telehealth enables patients to receive ENT specialist consultations through remote communication, which eliminates the requirement of distant travel. The healthcare system benefits patients who have restricted movement, together with senior citizens and people who need ongoing medical checks [57,58].

Implementing e-health systems in ENT practice results in improved time management for patients and their healthcare providers. Virtual consultations help patients receive their appointments faster while enabling faster diagnosis and more efficient follow-up care. The flexible scheduling system allows physicians to manage their time better while decreasing the administrative work that comes from traditional office visits [59]. Patients experience better care satisfaction while their daily activities remain uninterrupted because of this system. The analysis of costs represents a fundamental advantage. The reduction of healthcare expenses occurs because e-health decreases the requirement for transportation and hospital visits and eliminates the need for in-person appointments for patients and healthcare providers. Remote monitoring tools and asynchronous consultations help medical staff identify complications early which enables timely interventions to prevent condition escalation and decrease emergency visits [60]. Through e-health patients receive consistent and complete management of chronic ENT conditions including hearing loss and allergic rhinitis and sinusitis and obstructive sleep apnea. The combination of remote audiometry and CPAP compliance monitoring and symptom-tracking apps enable healthcare providers to monitor patients in real time while adjusting treatment plans according to individual needs [61]. Better disease control combined with improved patient therapy adherence leads to enhanced quality of life for patients[62].

E-health also supports multidisciplinary collaboration. ENT specialists use digital platforms to exchange imaging data and audio recordings and video laryngoscopy results with other medical specialists which improves both diagnosis and coordinated treatment approaches. The combination of complex head and neck cancer cases with patients who have multiple health conditions requires this feature for proper coordinated care [55,63]. E-health platforms demonstrate both scalability and adaptability which enables fast implementation during public health emergencies like the COVID-19 pandemic. The implementation of digital healthcare solutions enables continuous patient care which helps prevent disease progression while providing reassurance to patients and maintaining healthcare system operational capacity [64,65].

E-health implementation for otorhinolaryngology practice brings many positive aspects but it also brings multiple difficulties and constraints. The main drawback of e-health implementation is its inability to perform physical assessments [66]. ENT diagnosis heavily depends on physical examination techniques including otoscopy and nasal endoscopy and laryngoscopy which need specialized tools and skilled operators that telehealth platforms cannot replace. The absence of direct physical examinations results in both missed and incorrect diagnoses of conditions [67]. The digital divide continues to affect different patient groups who lack proper e-health service access. The accessibility of e-health services strongly depends on three factors which include internet connectivity and digital literacy capabilities and device compatibility. The required technology for virtual consultations creates obstacles that elderly patients together with people from low-income backgrounds and residents of remote locations face difficulty using. Health inequalities grow worse because of this disparity which reduces the complete benefits of e-health advancements for vulnerable populations. The security of patient information along with cybersecurity threats pose major risks to data protection systems. The digital transfer and storage of patient information creates elevated risks of data breaches as well as unauthorized access and misuse of sensitive medical data. Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR) regulations present compliance challenges that require constant security infrastructure development and monitoring to achieve compliance [68–70].

1.4. Translation of telemedical solutions into clinical application

Telemedicine applications have been successfully used by various segments of the clinic for years. The most common areas of application include teledermatoscopy, teleradiology, telemental health and teleopthalmoscopy. Increasingly, healthcare units are utilizing

teleradiology, telecardiology and tele-intensive-care-unit services that monitor patients 24 h per day and alert on-site healthcare providers [71]. Telemedicine strategies have been shown to play an increasing role in ear disease diagnosis. The use of telemedicine solutions is beneficial for both the patient and the otorhinolaryngologist: as the medical examination can be performed even at home or in primary care, the waiting time and the burden on the hospital care system can be reduced, and the diagnosis can be made faster, even in case of pandemic situations [72]. With the advance of technology in the field of otorhinolaryngology, several diagnostic devices have evolved over time. The development of the video otoscope brought the possibility of using the smartphone as an important diagnostic tool in clinical practice. Smartphone otoscopes can record images of comparable diagnostic utility to conventional otoscopy coupled with a custom software app, enabling the capture of video and static images in real time that may be stored and transmitted to healthcare specialists using wireless communication for remote diagnosis and management (Figure 3) [73]. Using them, healthcare specialists can quickly and easily screen out serious symptoms such as bleeding and pus, which need emergency intervention. Previously, several studies already discussed the clinical assessment of video-otoscopy in remote diagnosis by specialists [66,74]. The novelty of our work lies in focusing the utilization of telemedicine at the primary care level. The burden of higher (III) progressiveness levels can be reduced in this way. The smartphone and the otoscope that can be connected to it are a relatively inexpensive, easily accessible otorhinolaryngology diagnostic tool in the hands of the primary care provider, which greatly supports diagnostics and documentation, and last but not least, helps communication between the primary care provider and the specialist. By remote education of family doctors, their gatekeeper role could be increased. Moreover, it can be a suitable tool for family doctors to examine bedridden patients at home.

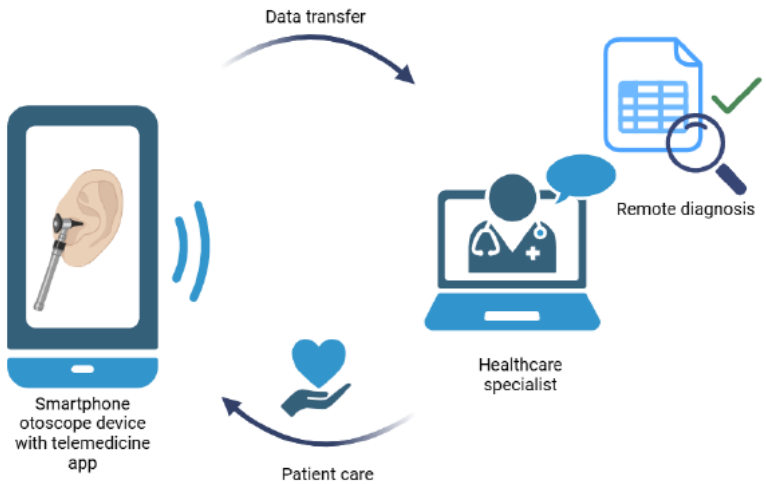

Figure 3. Schematic presentation of otorhinolaryngological remote diagnosis and management

2. Aims

The main purpose of this research is to assess the clinical diagnostic and therapeutic accuracy of telemedicine software in relation to conventional standards through detailed statistical analysis of matching diagnoses and therapies in clinical data. The thesis also aims to examine the effects of regulatory frameworks on the development, approval and implementation of telemedical and medical technology products including medicinal products, standalone medical devices and combined drug–device products. The thesis aims to integrate clinical performance data with regulatory analysis to provide a comprehensive understanding of the challenges and opportunities associated with the clinical evaluation and market integration of telemedicine technologies, thus contributing to more effective and safer innovation in digital healthcare.

Main objectives:

1. To analyze how product classification influences clinical trial requirements and post-market obligations.
2. Comparing clinical trial methodologies and regulatory frameworks for medicinal products and medical devices.
3. To evaluate the diagnostic accuracy of a telemedical video-otoscopic device.
4. To assess the therapeutic alignment between the recommended diagnoses provided by the telemedicine system and the factual diagnosis.
5. To conduct cross-tabulation and overlapping analysis of diagnosis and therapy data to understand the clinical relevance of non-exact matches and explore possible patterns of partial concordance.

3. Methodology

3.1. Analysis and comparison of clinical trial routes based on product category

The methodology to evaluate drug and medical device clinical trial differences and similarities requires analyzing the governing regulations through a comparative study of EU Regulation (EU) No 536/2014 for drugs and EU Regulation (EU) 2017/745 for medical devices by examining trial design and approval processes and ethical over-sight and transparency requirements. The analysis relies on process mapping to show procedural steps and regulatory actors and selected case studies from public databases (e.g., EudraCT, EUDAMED) to identify practical differences in trial implementation. The analysis draws additional insights from academic literature and regulatory reports and stakeholder perspectives when possible. The analysis aims to reveal regulatory convergence areas while explaining sector-specific limitations and adaptable elements.

3.2. Evaluation of the performed telemedical clinical trial

3.2.1. Applied telemedicine device and software

The telemedicine software developed by the University of Szeged was used for the study, which supports the transmission and analysis of otoscopic images and clinical data. The device consisted of a CE-marked optical unit applied (Cupris TYM smartphone otoscope device, Cupris Ltd., Somerset, UK) to a CE-marked smartphone and the software that operates the system, and was the subject of the test, as well as a detailed user guide. The device was used to record videos of the external auditory canal and the tympanum, and to record clinical data (symptoms, complaints) (Figure 4). The phone application transmitted the data to the examining physician, who analyzed the data, made a diagnosis and therapeutic recommendation and arranged the following visit.

Figure 4. Smartphone otoscopic device

3.2.2. Participants of the study

The study was conducted in accordance with the Declaration of Helsinki. It was approved by the Medical Research Council and the National Scientific and Ethical Committee (OGYÉI/1422/2020). Written informed consent was obtained from the patients or their parents/guardians before the study and participation was voluntary. The study included 103 patients aged 0–100 years with otorhinolaryngological complaints, and who have consented to the examinations. From January to May 2020, data were collected from patients with otorhinolaryngological complaints admitted at the Department of Oto-Rhino-Laryngology and Head-Neck Surgery, Faculty of Medicine, University of Szeged, based on the inclusion and exclusion criteria. The patients with ear complaints (mainly but not limited to earache, discharge from the ear, itching, and cerumen accumulation) were involved in the study, who communicated well with the investigator and could understand and comply with the requirements of the protocol and signed the informed consent. The exclusion criterion of the study was, on the one hand, the patient's withdrawal of informed consent at any time after being informed and signing, thereby suspending his or her participation orally or in written form. On the other hand, patients with poor general conditions, traumatic events or symptoms that may be directly life-threatening were excluded from the study, as determined by the investigator (e.g., cerebrospinal fluid leakage or massive bleeding). Further exclusion reason was any medical condition which, in the investigator's opinion, may have compromised the patient's health and/or contraindicate the conducting of the study, or the patient's participation was suspended for any reason according to the investigator.

3.2.3. Study protocol

Patients who visited the Department of Oto-Rhino-Laryngology and Head-Neck Surgery or outpatient clinic were informed about the nature of the study before signing the informed consent forms. Then, the data necessary for the demographic data of recruited patients were recorded in the telemedicine software by a physician/nurse from primary care (who is not an otorhinolaryngologist specialist). After that, a static image or video (otoscopic recording) of the external auditory canal and the tympanum was recorded, uploaded into the telemedicine system and shared with a specialist (otorhinolaryngologist no. 1.) for selecting the proposed diagnosis in the telemedicine system based on the telemedicinal data. Parallel to that, the patient was physically examined by another independent specialist (otorhinolaryngologist no. 2.) who recorded the anamnesis with the same questions included in the telemedicine system, defined diagnosis, and recommended therapy from the optional list that was included in the telemedicine system. Finally, an individual expert (otorhinolaryngologist no. 3.) compared whether the diagnoses and the treatments made by the two methods were matching. In the case of the match, only one was assessed; however, if there was a difference, both were assessed. The study design algorithm is shown in Figure 5.

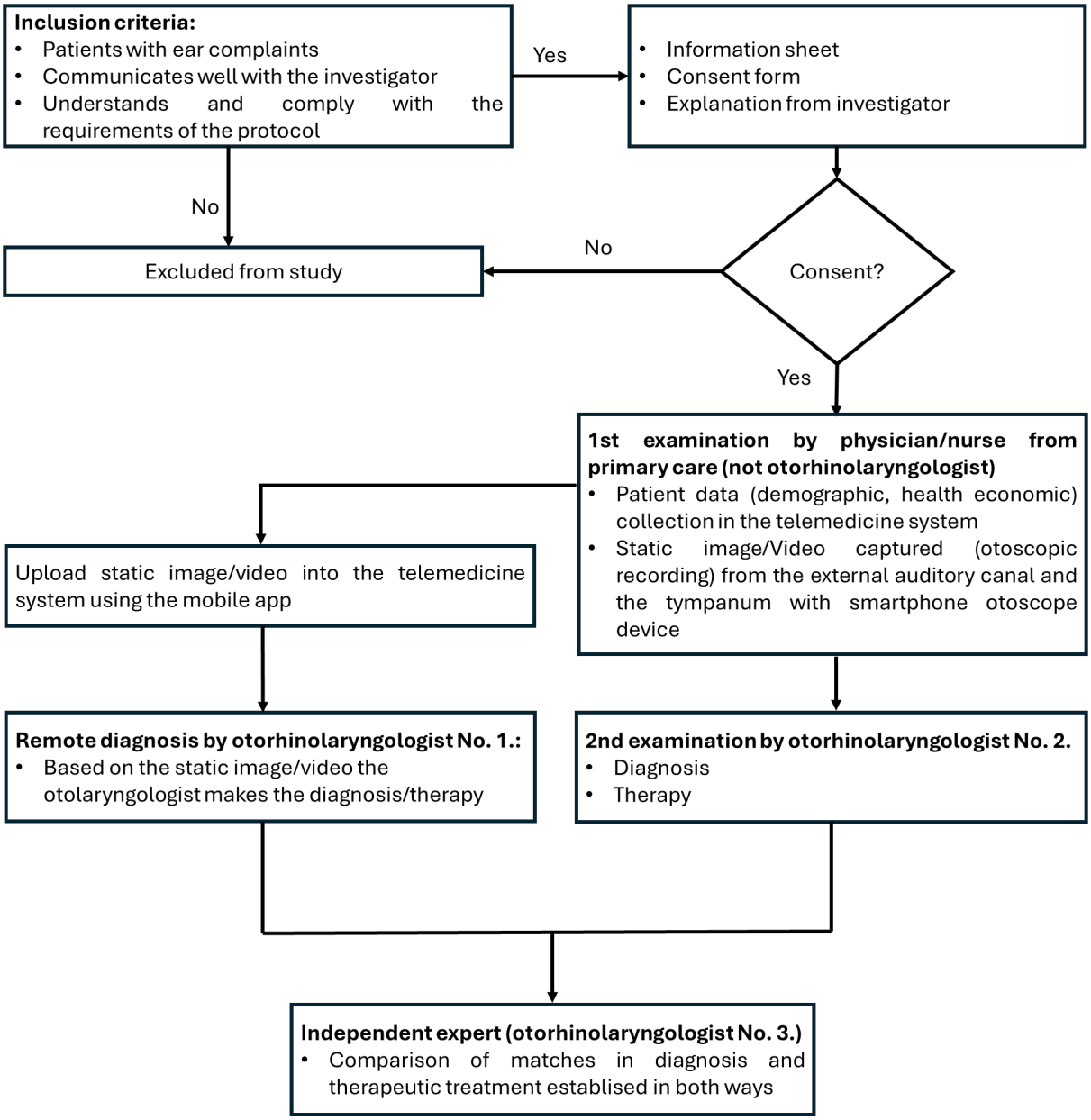

Figure 5. Study protocol flow diagram

3.2.4. Data analysis

The main aim of the study was to compare the consistency of the diagnoses and therapeutic treatments made by remote diagnostics and on-site specialists. The primary target variable was the “ratio of matches”, which defines the percentage result of matches compared to total number of cases. Principally, the diagnosis was selected based on the International Statistical Classification of Diseases and Related Health Problems (ICD). The two study results are considered matching if the same diagnosis was selected from the drop-down menu and the main group (first level) of therapy was the same (not at the active pharmaceutical ingredient and dose level), and was confirmed by the independent expert. For demographic data evaluation, descriptive statistics provided the number of cases, the mean value, the standard deviation, the minimum, the median and the maximum values. In the category variables, the number of cases and the frequency of occurrence were given.

The primary efficacy analysis examined the ratio of the matching therapies and diagnoses. The ratios and the 95% confidence intervals are given, and the Wald test was used to study the matches above 90%. The statistical significance level was 0.05. The secondary efficacy analysis examined the ratio of matching therapies and matching diagnoses. The ratios and the 95% confidence intervals are given, and the Wald test was used to study the matches above 90%. The statistical significance level was 0.05. Descriptive statistical methods were applied for further analyses (same diagnosis, different therapy, matches per each optional diagnosis).

The ratio of different therapies and diagnoses and the ratio of matching and overlapping therapies and diagnoses were studied. These ratios and the 95% confidence intervals are provided.

4. Results

4.1. Comparative analysis of the EU clinical trials based on product category

The approval process for healthcare interventions diverges substantially between medical drugs and medical devices and drug-device combinations. Each product category operates under separate regulatory structures alongside its own clinical testing procedures and market monitoring requirements. The appropriate development of study protocols depends on these distinctions to meet regulatory standards and achieve market authorization. This paper investigates the detailed clinical and regulatory requirements of these three product types by using a structured comparison format.

The European Union governs medicinal products through Clinical Trials Regulation No. 536/2014 (CTR) which standardizes clinical trial assessment and supervision across all member states. The new Clinical Trial Information System (CTIS) under this regulation centralizes application and monitoring processes between member states. Medical devices now operate under the MDR 2017/745 since it replaced the MDD. The MDR prioritizes safety and performance alongside post-market surveillance yet grants different trial design flexibility based on device risk classifications. Products that combine drugs and devices must navigate two separate regulatory systems. The regulatory authority that has primary jurisdiction depends on which therapeutic effect component (drug or device) dominates the therapeutic effect. The approval process becomes more intricate because developers need to examine both aspects during development.

A CTA for drugs needs to be submitted through CTIS where it requires both regulatory and ethics board approvals. The centralized evaluation process of EU member states allows consistent assessment of risks and benefits throughout the region. A clinical investigation application must be submitted by sponsors to both the national competent authority and the relevant ethics committee for medical devices. The assessment process for member states and device classifications differs with Class III devices receiving the most stringent evaluation. The submission process for combined products requires coordinated strategies because the regulatory pathway depends on the PMOA but involves assessments from both drug and device regulators. The dual regulatory oversight results in longer approval timelines and increased paperwork requirements.

All investigational drugs for medicinal products must undergo thorough assessment because there exists no trial-based risk classification system. The risk level of investigational drugs

stands as an established assumption because they inherently present considerable dangers. Medical devices receive their risk classification through an assessment of invasiveness alongside duration of use and potential harm to patients which results in four risk classes (I, IIa, IIb, III). The regulatory review intensity together with necessary clinical study requirements depends on the product classification. The regulatory requirements for combined products become more stringent because their dual nature and complex structure results in elevated combined risks from the drug and the device.

The standard drug development process consists of four sequential clinical phases. The first phase of drug development tests safety and pharmacokinetics using healthy volunteers but Phase II investigates efficacy in a small patient population while Phase III conducts large randomized controlled trials (RCT) for both efficacy assessment and adverse reaction monitoring and Phase IV performs post-market surveillance. Medical devices lack traditional phased development since they need to demonstrate safety and performance through feasibility studies before moving to pivotal trials. The assessment of combined products requires innovative trial approaches that evaluate drug efficacy together with device performance because this dual evaluation is crucial for verifying integrated product functionality.

The standard research method for drugs involves RCTs with blinding and placebo control whenever ethical requirements allow it. Medical devices require non-standard testing approaches because they need usability assessment studies that compare devices to each other since blinding and placebo use is either unfeasible or unethical for certain devices. The clinical trials for combined products demand a complex approach that merges RCT principles with device usability and technical performance assessment methods. The clinical studies for these products become more intricate because they need to handle rich data sets. The sample sizes between these categories differ substantially from one another. The patient numbers in drug trials extend from hundreds up to thousands of participants throughout different phases of testing. The trial population for medical device evaluations remains smaller especially during feasibility assessments and initial product evaluations. Combined products require more participants in clinical trials because they need to show drug efficacy together with device performance in multiple clinical contexts.

The evaluation of drugs depends mainly on pharmacokinetic data along with efficacy results and safety results. Most of these assessment metrics exist as standardized numerical measures which span all relevant conditions. The primary evaluation criteria for devices consist of performance alongside usability and functionality and occasional assessment of procedural

success. The selection of endpoints for combined products demands careful planning to verify that both drug-related and device-related data maintain sufficient strength for regulatory approval purposes. The assessment of endpoints through composite outcomes together with dual primary endpoints creates complexity in statistical analysis and trial design.

The EMA needs 12 to 18 months to approve drugs particularly when assessing new substances. The review process for medical devices classified as I and IIa moves at a faster pace compared to other classes. Class III devices need to undergo an extended and detailed assessment through notified bodies for approval. The regulatory review of combined products takes longer than usual because these products need to meet standards from EMA as well as requirements from notified bodies or competent authorities. The combination of regulatory requirements becomes complex because it makes it difficult to synchronize evaluation schedules while meeting all necessary standards.

Pharmacovigilance requires drugs to report all adverse drug reactions (ADRs) as a mandatory requirement. Devices need to implement systems for detecting and reporting technical failures as well as usability concerns and safety incidents. The post-market surveillance system for combined products requires integration to properly monitor both ADRs and device-related events. The combined risk monitoring process needs synchronized data systems together with multidisciplinary expertise to handle risks effectively.

Manufacturing standards also diverge. Medical products need to follow GMP guidelines which maintain product consistency while ensuring purity and pharmaceutical standards compliance. The production of medical devices occurs under ISO 13485 which represents a dedicated QMS for medical devices. The manufacturing process for combined products needs to meet both GMP standards and ISO 13485 requirements which presents significant challenges for manufacturers who lack experience in both domains.

To conduct drug studies investigators must be licensed medical doctors because pharmacological interventions present both risks and complexities. Trials for medical devices with low risk can be performed by nurses or audiologists but require other healthcare professionals. The combination of pharmaceuticals and medical devices always necessitates physician investigators because of their need to handle pharmacodynamic aspects and drug safety alongside device operational considerations.

Most drugs produce systemic effects which impact the entire circulatory system and nervous system. Devices function through localized mechanisms which concentrate their effects on

particular organs. Combined products work through drug delivery systems which use medical devices to perform both drug administration and device-specific functions. The dual nature of combined products needs thorough investigation to understand how different components work together or potentially affect each other.

The ethical use of placebo controls in drug trials follows standard practice during most early phase studies. Medical device placebo controls remain scarce because ethical and practical reasons make sham surgeries or inactive devices unsafe. Placebo control for the drug component in combined products is feasible yet ethical justification is required for sham device inclusion when such procedures present invasive or risk-bearing aspects. A summary of the differences found during the analysis can be found in Table 3.

Table 3. Comparative summary of clinical trials for medicinal products (drugs), medical devices, and combined drug–device products. Abbreviations: CTR—Clinical Trials Regulation; MDR—Medical Device Regulation; CTIS—Clinical Trials Information System; EMA—European Medicines Agency; RCT—Randomized controlled trials; GMP—Good Manufacturing Practice; ISO—International Organization for Standardization.

Aspect	Drug	Medical device	Combined drug-device product
Regulation	CTR No. 536/2014	MDR 2017/745	Dual regulation: primarily CTR or MDR depending on primary model of action
Approval process	CTA via CTIS (regulatory and ethics approval)	Clinical investigation application with a submission to the competent authority and ethics committee	Coordinated submission based on the primary mode of action
Risk classification	No formal trial-based classification, as all investigational drugs must undergo a strict review	Classified as I, IIa, IIb, and III based on invasiveness and risk	Risk driven by both drug safety profile and device classification (usually elevated)
Clinical trial phases	Following Phase I–IV	Follows feasibility and pivotal studies	May include hybrid trial phases combining

			tests for drug efficacy and device performance
Study design	RCTs	Flexible, comparative studies	RCTs with embedded device usability/performance metrics
Sample size	Hundreds to thousands of patients	Dozens to hundreds	Depends on both drug efficacy and device-specific endpoints
Clinical endpoint	Pharmacokinetics, efficacy, and safety	Device performance, usability, functionality	Based on the assessment of both drug and medical device performance
Regulatory review time	12–18 months until EMA approval	Faster for low-risk devices, whilst Class III requires rigorous notified body assessments	Can be prolonged due to dual evaluation
Post-market surveillance	ADR monitoring	Device failure and usability issues monitoring	Requires integrated vigilance system covering both ADRs and device incidents
Manufacturing requirements	GMP	ISO 13485 (Medical Device QMS)	Must comply with both GMP and ISO 13485
Investigator requirements	Medical doctor	Healthcare professional	Medical doctor
Interaction with the human body	Usually works systematically	Usually works locally	Usually combined systemic and localized effects
Need for placebo control	Standard	Rare or unethical	Standard for the drug part, but ethically it should be justified for the device part

4.2. Evaluation of the clinical trial performed on the oto-videoscopic remote diagnostic system

4.2.1. Demographic and basic characteristics

One hundred and three (103) patients were enrolled in the study: 54 females (52%) and 49 males (48%) with an average age of 45.5 ± 19.57 years (range, 15–96 years) with a median age of 43.5 years. The cohort was predominantly composed of adults, the median age was 43.5 years. Regarding the travel distance of the patients, we found that the involved patients traveled an average of 12.9 km between their residence and the clinic, most of them by car (31.1%). Moreover, due to the otorhinolaryngological examination, 39.8% of the patients had lost working hours, an average of 2.7 h (SD, 1.85). Telemedicine solutions offer a suitable alternative to reduce travel distance, time and costs, as well as the loss of working hours. Using a smartphone otoscope device, the patient or their relative was able to capture static images or video from the affected ear canal at home easily and comfortably, and it provided for establishing a remote diagnosis to the healthcare specialist through the telemedicine software.

4.2.2. Number of matches in the diagnoses together

The telemedicine software underwent simultaneous diagnosis-therapy matching evaluation during its primary analysis. The telemedicine software received its clinical accuracy and utility evaluation through the assessment of diagnosis-therapy matching as a primary quality metric. The primary analysis evaluated diagnosis and treatment decisions together as a single outcome to verify that telemedical system recommendations matched clinical diagnoses. The evaluation revealed that 56 out of 103 reviewed cases (54.4%) showed complete agreement between diagnosis and therapy. The observed match rate fell below the pre-defined reference value of 90%, which represents the expected agreement level in traditional face-to-face clinical encounters. The Wald one-sample proportion test produced a z-value of −7.260 and a two-sided p-value of <0.001 which showed that the observed match rate was significantly lower than expected (Table 4). The 95% confidence interval (CI) for the match rate ranged from 44.7% to 64.0%, which demonstrated the significant difference from the expected standard.

Table 4. Matching diagnoses and therapies—test statistics.

One-Sample Proportion Test									
		Observed				Asymptotic Standard Error	Z	Significance	
	Test Type	Success	Trials	Proportion	Test Value			One-Sided *p*	Two-Sided *p*
Are the diagnoses and the therapies matching? = Matching	Wald	56	103	0.544	−0.356	0.049	−7.260	<0.001	<0.001
	Wald (Continuity Corrected)	56	103	0.544	−0.356	0.049	−7.161	<0.001	<0.001

The continuity-corrected Wald test which adjusts for sample size and conservatively estimates the significance level yielded similar results ($z = -7.161$, $p < 0.001$) confirming the robustness of the finding. The significant difference between the two results indicates a fundamental problem with either the software's clinical impression to treatment decision conversion process or the therapeutic algorithms used in remote practice. Several potential contributing factors may account for this result. The decision-making process became inconsistent because users with different clinical experience levels especially generalists instead of specialists performed the assessments. The diagnostic precision suffered because telemedicine restricted visual examination and eliminated tactile feedback and real-time auscultation capabilities. The software's decision support system which operates through algorithms might not have the necessary capabilities to handle the complete range of clinical situations found in otorhinolaryngology practice.

The low match rate between remote and in-person diagnoses creates significant concerns about patient safety and the dependability of remote healthcare delivery in the specific field of otolaryngology that requires detailed visual and spatial evaluations. The study results do not prove that telemedicine is useless but demonstrate the requirement for careful deployment and continuous system improvement and validation. Future studies need to investigate how user-related elements (training and experience and practice setting) and technological aspects (image clarity and audio quality and interface design) affect clinical precision. Additional research with bigger participant numbers and standard in-person assessments would offer detailed insights about this telemedical system's capabilities and weaknesses.

4.2.3. Number of matches in the diagnoses individually

The secondary analysis of telemedicine software evaluated diagnostic agreement precision between telemedicine assessments and reference evaluations without considering treatment decisions. The research aimed to assess whether the diagnostic features of the software exceeded the combined diagnostic-treatment matching results from the primary analysis. The diagnostic concordance rate reached 76.7% when researchers identified matching diagnoses in 79 out of 103 evaluated cases. The 95% confidence interval for this rate ranged from 68.5% to 84.9%, indicating a relatively high level of agreement, though still lower than the predefined reference standard of 90%. The one-sample Wald test evaluated the observed proportion against the 90% threshold and produced a z-score of −3.193 and a two-sided p-value of 0.001 which confirmed the observed agreement fell below expectations. The continuity-corrected version of the test produced a z-score of −3.077 and a p-value of 0.002 which supported the statistical significance of this deviation (Table 5).

Table 5. Matching diagnosis – test statistics

One-Sample Proportion Test									
		Observed				Asymptotic Standard Error	Z	Significance	
	Test Type	Successes	Trials	Proportion	Test Value			One-Sided *p*	Two-Sided *p*
Are the diagnoses matching? = Matching	Wald	79	103	0.767	−0.133	0.042	−3.193	<0.001	0.001
	Wald (Continuity Corrected)	79	103	0.767	−0.133	0.042	−3.077	0.001	0.002

The telemedicine software demonstrates acceptable diagnostic abilities yet it does not achieve the diagnostic standards found in conventional clinical practice. The software demonstrates promising results because it correctly identifies more than three-quarters of cases despite the challenges of remote assessment, including limited visual fields and missing physical examinations and inconsistent image or video quality. The moderate diagnostic agreement level could stem from multiple factors including the nature of assessed conditions and symptom clarity and healthcare professional experience with the system. The system performs better with diagnoses that have visible indicators or well-defined symptoms but struggles with ambiguous or complex cases that need physical examination tools.

The software demonstrates positive potential for clinical use because it achieves a 76.7% diagnostic match rate even though it falls short of the 90% threshold. The results indicate that the telemedicine platform functions well as an initial diagnostic instrument which helps identify typical ENT conditions to direct further medical actions including specialist referrals or direct in-person assessments. The growing use of telemedicine in rural and underserved areas and mobility-limited populations makes even moderate diagnostic accuracy highly beneficial for clinical practice.

The result provides opportunities to develop specific enhancements. The diagnostic algorithms need improvement alongside standardized data capture procedures and user training programs to enhance diagnostic reliability. The generalizability of these findings requires further investigation through studies that include more patients with diverse medical conditions. The system's true performance would become more apparent when more cases are included because the proportion estimate confidence interval would decrease.

The diagnostic agreement rate in this study fell below the expected 90% threshold but demonstrated strong diagnostic value for telemedical applications. The software demonstrates its ability to provide meaningful diagnostic support for remote medical practices especially in otorhinolaryngology because most conditions can be identified through visual assessment. The diagnostic accuracy gap between remote and in-person assessments requires ongoing development and training to establish telemedicine as a safe and effective diagnostic alternative.

4.2.4. Number of matches in the therapies individually

The second part of secondary analysis evaluated therapy selection accuracy independently from diagnostic assessments to determine whether treatment recommendation mismatches lowered the overall match rate from the primary analysis. The investigation demonstrated that only 61 of the 103 evaluated cases showed therapy recommendations from the telemedicine platform matching the reference standard treatments. The therapy matching rate in this evaluation reached 59.2% while the 95% confidence interval spanned between 49.7% and 68.7%. The predefined reference threshold of 90% matching demonstrates a substantial clinical and statistical discrepancy. A one-sample Wald test proved that this difference was statistically significant because it produced a z-score of −6.356 with a two-sided p-value of <0.001 (Table 6). The continuity-corrected Wald test provided a conservative estimate that indicated a highly significant result ($z = -6.256$, $p < 0.001$).

Table 6. Matching therapy – test statistics

One-Sample Proportion Test									
		Observed				Asymptotic Standard Error	Z	Significance	
	Test Type	Successes	Trials	Proportion	Test Value			One-Sided *p*	Two-Sided *p*
Are the therapies matching? = Matching	Wald	61	103	0.592	−0.308	0.048	−6.356	<0.001	<0.001
	Wald (Continuity Corrected)	61	103	0.592	−0.308	0.048	−6.256	<0.001	<0.001

The results demonstrate that therapy selection discrepancies caused the reduced matching rate found in the primary combined analysis instead of diagnostic inaccuracies. The diagnostic agreement reached 76.7%, but the therapy match rate remained below 59.2%, which indicates a problem with transforming diagnostic findings into suitable treatment choices in telemedicine settings. The software's decision support algorithms and user interpretation differences and regional treatment protocols used as standards might be the reasons behind this discrepancy. The selection of treatments beyond diagnosis depends on patient medical history and existing conditions along with drug interactions and professional clinical expertise that may not be fully represented in remote consultations.

The remote therapeutic decision-making process appears to have significant clinical completeness issues particularly in otorhinolaryngology since treatment options differ significantly based on minor clinical details. The suggested therapy might not fully account for individual patient factors or use algorithms that are too general when the diagnosis is properly identified. Antibiotic stewardship together with choices between topical and systemic treatments and surgical referral decisions require specific contextual information which proves difficult to obtain or interpret through remote consultations. The lower rate of treatment matches demonstrates the need to establish distinct criteria for evaluating diagnostic versus therapeutic performance of telemedicine systems. Therapy recommendation engines require both clinical guidelines and physician judgment as well as localized care practices to produce effective results even though diagnostic support tools work well with observable symptoms and images. The complex nature of treatment recommendations creates a higher probability of mismatches despite good diagnostic agreement.

The system evaluation of these findings indicates particular areas that need improvement in the telemedicine software. Advanced clinical decision support systems that incorporate contextual information and patient-specific data should be integrated to improve the system. Treatment recommendation pathways should be made clearer through automated prompts that deliver evidence-based suggestions that match diagnostic outputs to improve therapeutic accuracy. User training improvements specifically aimed at treatment selection for remote care can help reduce this performance difference. The therapeutic decision-making process depends on both patient and provider interactions. Treatment decisions in conventional care environments occur through patient-provider dialogues that consider individual preferences together with tolerance levels and earlier treatment outcomes. The standardized workflow and preconfigured options of telemedical models make it challenging to duplicate these specific treatment details. Telemedicine platforms can generate personalized recommendations by integrating patient-reported outcomes with medication history and previous treatment efficacy data.

4.2.5. Number of matches in the diagnoses in the case of different therapies

The following level of secondary analysis focused on the 79 patients who had their diagnoses verified to assess treatment decision agreement between accurate diagnoses. This evaluation analyzed the relationship between achieved diagnostic agreement and improved therapeutic choice consistency. 79 participants showed therapy matching in 56 cases (70.9%), but 23 patients (29.1%) received different therapy recommendations than the reference standard (Table 4). The data reveals an important pattern because diagnostic alignment increased the chances of therapy alignment, yet did not ensure complete alignment. The therapy recommendations for 30% of patients who received accurate telemedicine diagnoses did not match the reference standard, indicating a therapeutic-planning disconnect in telemedical workflows.

The cross-tabulation in Table 7 demonstrates the connection between diagnosis and treatment agreement through a series of diagnostic and therapeutic match and mismatch categories. The 24 patients with incorrect diagnoses had a 20.8% match in therapies but 79.2% of them received wrong therapy recommendations. Treatment choices align with diagnostic accuracy as expected because healthcare providers base their decisions on diagnostic information. The presence of therapy matches in 20.8% of misdiagnosed cases indicates that therapeutic choices occasionally align with correct standards because different treatment guidelines might overlap between potential diagnoses.

Table 7. Matching diagnoses and therapies – cross table

			Are the Therapies Matching?		Total
			Non-Matching	Matching	
Are the diagnoses matching?	Non-matching	Count	19	5	24
		% (Are the diagnoses matching?)	79.2%	20.8%	100.0%
		% (Are the therapies matching?)	45.2%	8.2%	23.3%
	Matching	Count	23	56	79
		% (Are the diagnoses matching?	29.1%	70.9%	100.0%
		% (Are the therapies matching?)	54.8%	91.8%	76.7%
Total		Count	42	61	103
		% (Are the diagnoses matching?)	40.8%	59.2%	100.0%
		% (Are the therapies matching?)	100.0%	100.0%	100.0%

The 79 patients who received accurate diagnosis matches showed 56 patients (70.9%) with corresponding therapy matches which proved the positive relationship between correct diagnosis and proper treatment. The telemedicine system's therapeutic recommendation engine faces limitations because 29.1% of patients received correct diagnoses but incorrect treatments. These treatment mismatches probably resulted from sources other than diagnostic accuracy because they involved differences in clinical thresholds and unrecorded patient factors and discrepancies in guideline implementation by the software. The data shows that therapy matches occurred in 91.8% of the cases where diagnoses were accurate. Most therapy mismatches happened in patients with correct diagnoses because more than half (54.8%) of all therapy mismatches occurred in this group. These findings support the hypothesis that the software's therapeutic component is less advanced than its diagnostic functionality. The observed patterns show diagnosis functions as a major treatment influencer yet other factors beyond diagnosis impact telemedicine treatment choices. The software requires better decision-support logic because therapy mismatches occur frequently even when diagnostic agreement exists. The execution of treatment algorithms needs to use diagnosis as a foundation while considering symptom severity together with patient preferences and contraindications and following local clinical practice guidelines. Treatment protocols in otorhinolaryngology show wide variations despite sharing the same diagnosis because patients receive either conservative or surgical care for conditions like tonsillitis and otitis media.

The therapeutic component of the telemedicine software requires the development of adaptive evidence-based treatment recommendations according to the collected data. Clinical

decision trees and software updates based on new guidelines together with clinician override capabilities that include justifications would improve accuracy. The application of software outputs by clinicians can be improved through training programs along with feedback systems which help them handle unusual patient cases. The data in Table 7 shows diagnostic accuracy enhances therapy correctness yet significant work remains to achieve consistent diagnostic-therapeutic alignment. The establishment of a diagnostic-therapeutic link remains vital for achieving better reliability and safety in telemedicine platforms. Future software development should aim to enhance therapeutic pathways through multidisciplinary partnerships between clinicians and informatics specialists and software developers to achieve both evidence-based precision and clinical adaptability.

4.2.6. Matching by optional diagnosis

The secondary analysis reached its advanced stage to evaluate how well the software matched both diagnoses and therapies with the optional diagnoses it generated. The software generates optional diagnoses through algorithmic processing of otoscopic images and patient symptoms and structured input data. The analysis served two purposes: it evaluated the diagnostic reliability of the telemedicine tool for each disease category and it determined if accurate condition diagnosis led to equivalent accurate therapy recommendations. The detailed analysis reveals important information about how the software performs in treating different otologic pathologies.

The matching ratios for diagnoses and therapies across 21 diagnostic categories are presented in Table 8. The table shows matching case proportions together with 95% confidence intervals and raw frequency counts. The results are divided by diagnostic label to assess software performance at both the aggregate and individual disease condition levels. The evaluation of software performance requires condition-specific analysis because otologic pathologies present different levels of diagnostic and therapeutic complexity ranging from simple recognizable cases with standard treatment to complex cases needing individualized management.

Table 8. Diagnosis and therapy matching ratio by optional diagnoses

Optional Diagnosis	Are the Diagnoses Matching? Matching				Are the Therapies Matching? Matching			
	N	Valid N%	95.0% CI Lower	95.0% CI Upper	N	Valid N%	95.0% CI Lower	95.0% CI Upper
Perforation of the tympanic membrane, unspecified	2	100.0%			2	100.0%		
Other otitis externa	1	100.0%			1	100.0%		
Other	2	40.0%	9.4%	79.1%	1	20.0%	2.3%	62.9%
Otalgia	1	33.3%	3.9%	82.3%	1	33.3%	3.9%	82.3%
Eustachian salpingitis	12	75.0%	50.9%	90.9%	7	43.8%	22.2%	67.4%
Tinnitus	3	75.0%	28.4%	97.2%	3	75.0%	28.4%	97.2%
Hearing loss, unspecified	3	50.0%	16.7%	83.3%	5	83.3%	44.2%	98.1%
Acute tympanic membrane inflammation	1	100.0%			0	0.0%		
Acute suppurative otitis media	1	25.0%	2.8%	71.6%	1	25.0%	2.8%	71.6%
Acute serous otitis media	4	36.4%	13.7%	65.2%	3	27.3%	8.3%	56.5%
Foreign body in the ear	3	100.0%			3	100.0%		
Sensorineural hearing loss—unspecified	0	0.0%			1	100.0%		
Chronic serous otitis media	0	0.0%			1	33.3%	3.9%	82.3%
Chronic tubotympanic suppurative otitis media	1	33.3%	3.9%	82.3%	1	33.3%	3.9%	82.3%
Impacted cerumen	26	83.9%	68.2%	93.6%	27	87.1%	72.2%	95.5%
Otitis media, unspecified	1	10.0%	1.1%	38.1%	4	40.0%	15.3%	69.6%
Disorder of external ear, unspecified	1	50.0%	6.1%	93.9%	1	50.0%	6.1%	93.9%
Nonsuppurative otitis media, unspecified	0	0.0%			1	100.0%		
Otitis externa maligna	5	83.3%	44.2%	98.1%	3	50.0%	16.7%	83.3%
Otitis externa, unspecified	30	78.9%	64.2%	89.5%	16	42.1%	27.5%	57.9%
Noise effects on the inner ear	0	0.0%			1	100.0%		

The telemedicine system produced more optional diagnoses in conditions where Otitis externa (n = 30), Impacted cerumen (n = 26), Eustachian salpingitis (n = 12), and Otitis externa maligna (n = 5) appeared — and the diagnostic matching rate exceeded 75% with strong validity support. The diagnostic matching rate for Impacted cerumen reached 83.9% (95% CI: 68.2%–93.6%) and Otitis externa reached 78.9% (64.2%–89.5%) which indicates strong agreement between software assessments and the reference standard. The system demonstrates reliable diagnostic performance in detecting common conditions with distinct otoscopic features and minimal dependence on patient history or subjective symptoms.

The therapy matching rates for these conditions demonstrated lower and more inconsistent results compared to the diagnostic matching rates. The therapeutic agreement for Otitis externa reached 42.1% while Eustachian salpingitis showed a lower 43.8% agreement despite achieving a 75.0% diagnostic match rate. The study confirms previous research showing that diagnosis and therapy matching do not follow a direct linear relationship. The system demonstrates effective condition identification but fails to generate suitable treatment plans consistently because its decision-support algorithms or contextual inputs are limited.

The condition Impacted cerumen produced exceptional results because it achieved both high diagnostic (83.9%) and therapeutic (87.1%) match rates. The software demonstrates both diagnostic and therapeutic effectiveness when dealing with basic algorithmically simple conditions that have limited treatment choices such as ear irrigation and manual removal. The limited treatment options together with predictable clinical practices explain this consistent performance.

The analysis of diagnostic categories with small case numbers ($n < 5$) revealed large data variability which produced extensive confidence intervals for proportions. These findings must be interpreted with caution due to the limited statistical power. Acute tympanic membrane inflammation and Other otitis externa achieved perfect diagnostic and therapeutic agreement (100%) yet each result derived from one or two cases. Although the numbers seem impressive at first glance they do not provide generalizable results because they might represent statistical anomalies or selection biases.

The unspecified Otitis media condition received a diagnostic match rate of 10.0% which stood as one of the lowest rates throughout the entire dataset and its corresponding therapy match rate reached 40.0%. The software demonstrates classification and treatment decision-making weaknesses in ambiguous cases that present either overlapping symptoms or indistinct otoscopic features. The diagnostic match rates for Acute serous otitis media and Chronic serous otitis media reached 36.4% and 0.0% respectively because fluid-based middle ear conditions present challenges to remote identification and treatment. The diagnosis of these conditions requires pneumatic otoscopy or tympanometry for proper assessment because these essential tools cannot be used in video-otoscopic telemedicine.

The diagnostic agreement for Sensorineural hearing loss reached 0.0% but the therapy matching rate reached 100%. The treatment decisions made for these cases either occurred incidentally or the standard treatment approaches were so common that they did not depend on

accurate tele-diagnosis results. The lack of audiometric data in telemedicine settings makes it impossible to diagnose sensorineural pathology accurately because this explains the diagnostic failure.

The diagnostic categories showed inconsistent results between their diagnostic agreement and therapy agreement levels. The unspecified Hearing loss diagnosis received a 50.0% diagnostic agreement rate which correlated with an 83.3% therapy match rate indicating that although diagnostic specificity was weak the treatments followed standard care protocols. The diagnostic and therapeutic agreement rates for Otalgia and Tinnitus were moderate to high because these entries used symptoms instead of medical diagnoses. The simplicity of symptom-targeted treatments may work well for these cases but the variable results demonstrate the challenges of condition categorization in symptom-driven diagnoses.

The diagnostic-therapeutic cascade in telemedical systems presents a critical shortcoming because the relationship between diagnosis and treatment does not follow a direct path. The accuracy of diagnosis does not automatically lead to appropriate treatment because software makes decisions based on restricted contextual information. The diagnostic abilities of human clinicians go beyond basic inputs since they use historical information along with treatment response data and multiple existing conditions to create individualized treatment plans. The software-generated static pathways struggle to identify complex clinical details.

The findings in Table 8 demonstrate why telemedicine requires specific condition-based validation procedures. Developers along with regulators need to assess accuracy through detailed evaluations of specific disease categories instead of making general assessments. Immediate telemedicine implementation appears suitable for Impacted cerumen and Otitis externa conditions because they achieve high match rates in both diagnosis and therapy. Serous otitis media and sensorineural hearing loss along with chronic otitis media variants should have cautious deployment or need supplemental tools including remote audiometry and patient history modules for accurate care delivery.

The analysis demonstrates that different algorithms need specific adjustments for each condition. Diagnostic engines need therapeutic recommendation systems which should match their level of sophistication to include guideline-based variations and comorbid factors and patient preference elements. Real-time clinician review and automated alerts for therapy mismatch risk in hybrid models would enhance both safety and trust in remote care delivery.

Future research must increase the number of cases within low-incidence categories by using stratified sampling or enrichment strategies to achieve sufficient representation. The validation process should include expert panel reviews and patient outcome reports and cost-effectiveness studies to establish a strong foundation for telemedical adoption.

4.2.7. Overlapping in diagnoses and therapies

The evaluation of telemedicine system accuracy required further analysis to examine cases with clinical overlap when exact matches were not found. The evaluation method was required to identify meaningful partial agreements since they presented clinical importance despite incomplete matches. The medical field of otolaryngology shows overlapping symptoms and multiple possible treatments leading to acceptable clinical variability. Evaluating the utility of telemedical decisions requires analyzing overlapping diagnoses instead of demanding precise matches to generate more realistic results.

The research examined diagnostic and therapeutic matches for 103 patient cases even when the exact matches were not achieved. The results depicted in Figure 4 showed that 89 out of 103 cases shared diagnostic or therapeutic characteristics with gold standard even though they did not match exactly. The overall overlapping ratio reached 86.4% (95% CI: 79.8%–93.0%) showing that many non-matching cases still fell within acceptable clinical equivalence ranges.

The diagnostic overlap occurred in 91 out of 103 cases which led to an 88.3% (95% CI: 82.2%–94.5%) ratio. The high diagnostic overlap rate indicates that the telemedicine software chose diagnoses from the same etiological or anatomical group when it failed to match the reference standard diagnosis exactly such as selecting "acute otitis media" instead of "serous otitis media." The distinctions between these diagnoses do not significantly impact patient care which preserves practical diagnostic value.

The therapy overlap occurred in 97 out of 103 cases leading to a therapy overlap ratio of 94.1% (95% CI: 89.7%–98.7%). The software generated therapeutic options that fit within acceptable treatments for broader diagnostic categories in the majority of diagnostic discrepancies. The system recommends appropriate antibiotic treatment for both bacterial otitis externa and otitis media or provides ear cleaning recommendations suitable for multiple cerumen-related and inflammatory ear conditions.

The high overlap rates indicate that the telemedicine system maintains its clinical worth when it does not produce perfect diagnostic results. Real-world medical practice often involves

diagnoses that exist on a spectrum while small variations between classification terms do not trigger new treatment approaches. The use of overlapping categories demonstrates an awareness of clinical decision-making approaches that evaluate multiple diagnostic possibilities while initiating treatments based on observed symptoms rather than confirmed diagnoses.

The results of this analysis show that evaluating the software's performance through exact matching alone could produce underestimations of its clinical benefits. The addition of overlap metrics helps recognize that medical diagnosis involves multiple factors together with the natural uncertainties found during remote health evaluations. The system provides safe and reasonably accurate guidance to medical practitioners in most situations regardless of its failure to precisely match human expert decisions.

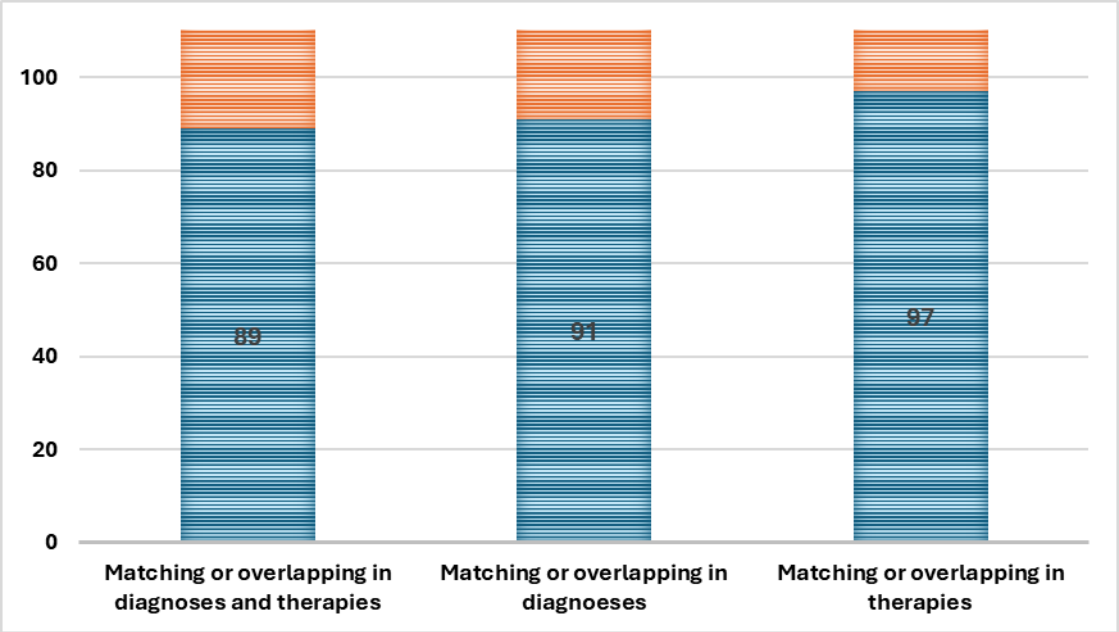

Figure 6. Number of cases with matching or overlapping diagnoses and/or therapies (n = 103).

5. Discussions

5.1. Comparison and analysis of clinical trials based on product category

The research development and regulatory planning of health technologies requires proper medical product classification between medicinal products and medical devices and combined drug-device products. This classification maintains its purpose beyond official administrative procedures. The chosen product category determines all aspects of regulatory procedures along with clinical trials methods and risk evaluations and manufacturing standards and post-market responsibilities. The increasing adoption of integrated medical technologies and multi-functional therapies in today's medical landscape makes selecting the appropriate product category more critical than ever.

A medicinal product which is usually a drug goes through a systematic development process following clinical trials regulation. The drug approval process requires drugs to pass through four clinical stages starting from Phase I to Phase IV which examine pharmacokinetics and effectiveness as well as safety aspects. Drug trials need extensive post-marketing adverse reaction surveillance following their completion of randomization and placebo control procedures with big participant numbers. Medical devices operate under separate regulations which organize them through Class I to Class III risk-based categories. The trial process for devices features more adaptability and uses various assessment methods which focus on usability together with mechanical performance and accuracy instead of requiring large patient numbers. The evaluation process and regulatory oversight for devices focuses on localized mechanical body interactions because devices operate differently from systemic biochemical processes.

The evaluation process of combined drug–device products like autoinjectors, drug-eluting stents and medicated wound dressings becomes complex because these products need to follow regulations from both medicinal and device categories. A product qualifies under medicinal or device regulation based on its main functional mechanism. The therapeutic outcome determines which regulatory framework takes precedence when the drug-based effect stands foremost while the device-based effect stands dominant. Although one regulatory framework leads the way it demands complete evaluation of all components from the other framework. The dual nature of these requirements demands manufacturers to fulfill both GMP standards and ISO 13485 specifications while developing studies which evaluate both drug performance and device effectiveness.

Initial development mistakes regarding product classification result in substantial time delays and additional submissions before regulatory approval is possible. A clinical study which fulfills drug assessment criteria but fails to meet device usability standards will produce results that do not meet device approval standards and vice versa. The evaluation process for hybrid products demands both drug efficacy testing through randomization and device performance evaluation through observation which adds complexity to trial protocols. The design of clinical trials faces major changes because combined products need larger participant groups and complex dual-endpoint analysis methods that reflect their dual nature.

The regulatory review period for medicinal products extends because of the thorough safety and efficacy tests required during approval processes. The review process for devices generally moves faster but Class III devices face extended review procedures despite these devices being considered high risk. The approval process for combined products stretches to its maximum duration because agencies need to conduct joint assessments or synchronized reviews. These prolonged approval periods create challenges for companies because they limit their market access. The intricate nature of classification becomes evident through post-market obligations. The pharmacovigilance systems of drugs serve to detect drug side effects as well as long-term safety concerns. Devices must implement performance failure tracking systems together with user error monitoring and product malfunction detection systems. The tracking of both risk types requires companies that produce combined products to merge their monitoring systems. The dual monitoring system makes quality management more complex while requiring companies to establish robust internal procedures.

The dual nature of the product determines all manufacturing requirements. The production of drugs follows GMP standards but devices must meet the requirements of ISO 13485 QMS. The combined product requirements demand that both manufacturing and quality processes fulfill the strict requirements of two parallel regulatory frameworks. The successful navigation of these dual pathways requires essential involvement from engineers together with pharmacists and clinical researchers and regulatory experts. Medical R&D product classification serves as a regulatory requirement but also functions as a fundamental element that determines the complete development and operational lifecycle of a product. The product category selection determines all aspects of therapeutic development and product lifetime. The correct category selection during this era of advanced integrated medical therapies provides regulatory clarity and supports trial efficiency and speeds up approval processes and safeguards patient safety.

Proper classification at the start of development serves as both best practice and essential requirement for innovation and compliance as well as commercial success.

5.2. Evaluation of the performance of the oto-videoscopic telemedical device

The thesis provides a comprehensive analysis of clinical evaluation and development processes across telemedicine and medical technology advancements. The analysis of clinical trial data through diagnosis and therapy matching reveals both obstacles and opportunities in telemedical applications. The diagnostic agreement rate reached 76.7% with 79 out of 103 cases meeting the benchmark (95% CI: 68.5–84.9%) indicating that telemedicine software demonstrates strong potential for remote diagnostics although it falls short of the ideal 90% concordance level. The therapy matching rate reached only 59.2% (61 out of 103 cases; 95% CI: 49.7–68.7%) which produced the low alignment observed between diagnoses and therapies during the primary analysis when only 54.4% of cases (56 of 103; 95% CI: 44.7–64.0%) matched exactly. The translation of diagnostic findings to suitable therapeutic actions proves challenging especially when using remote or telemedical methods.

The cross-tabulation analysis revealed that therapy matches existed in 70.9% of cases (56 of 79) that had matching diagnoses yet 29.1% (23 of 79) received non-matching treatments despite having agreed-upon diagnoses. Telemedicine decision-support tools need ongoing improvement to enhance the alignment between treatment recommendations and diagnostic outputs. The evaluation of optional diagnoses revealed differences in diagnostic and therapeutic match rates where common conditions like impacted cerumen and otitis externa exceeded 75% but rare conditions presented broad confidence intervals and typically low agreement percentages. Telemedicine software shows better performance with common diagnoses yet requires advanced clinical algorithms or expert input hybrid systems for handling infrequent and complex medical cases.

The evaluation of overlapping diagnoses and therapies within non-matching cases extends our comprehension of the situation. A combined matching or overlapping ratio of 86.4% (89 of 103 cases; 95% CI: 79.8–93.0%) emerged even when exact matches were not present indicating significant clinical significance and therapeutic appropriateness beyond basic concordance standards. The clinical utility of telemedical assessments proved strong in cases of non-matching diagnoses where 88.3% (91 of 103) of cases still showed matching or overlapping and in cases of non-matching therapies where 94.1% (97 of 103) of cases demonstrated potential utility despite direct match imperfections. The findings are particularly significant for

telemedicine practice because patients require to rely on partial or indirect data due to limited physical examination capabilities.

5.3. Application of telemedicine in otorhinolaryngology

E-health, telemedicine and telehealth have had significant practical application in otorhinolaryngology in the last few years. These technologies are currently being adopted in all the sub-specialties and are being used for remote assessment, diagnosis, monitoring and treatment of ENT disorders. Teleconsultations have emerged as an important aspect of outpatient ENT management. The use of virtual visits is appropriate for managing conditions like allergic rhinitis, sinusitis, laryngitis and follow-up care of benign growths. Patients are able to report their symptoms, send pictures or videos of the affected areas and get direction without having to come to the clinic. Virtual consultations enable the differentiation between urgent and non-urgent cases. For instance, a patient who presents with new hoarseness can be assessed via a video call, if there are worrisome features, the patient can be taken for an in person laryngoscopy [67,75,76].

Otology has been enhanced by the use of digital otoscopes which are used by the patient or the caregiver in the home or in the primary care clinics to take pictures of the tympanic membrane. These images can be sent to ENT specialists for analysis. It is most useful in pediatric practice as children have recurrent infections of the ear and early diagnosis and management is critical. Audiology services have also gone the remote way [77]. Tele-audiology is hearing screening, hearing aid programming, and vestibular assessment for patients in rural or hard to reach areas. Real-time audio calibration on platforms that support it ensures that quality and accuracy is achieved [76,78]. Telehealth is used more frequently for patients with chronic rhinosinusitis, nasal polyposis, and allergic conditions. The initial visit, as well as the subsequent check-ups to assess the patient's response to the treatment or compliance with the medication, can be done virtually. Through secure portals, patients usually send nasal endoscopy images or CT scans to enable clinicians to change the treatment plan. Further, digital smell testing kits and patient reported outcome measures have allowed for the remote diagnosis of anosmia or hyposmia—a symptom that gained public attention during the COVID-19 pandemic [64].

Dysphonia, vocal fold nodules, or muscle tension dysphonia patients with voice disorders are best managed through telemedicine in virtual voice therapy. SLPs, in conjunction with otolaryngologists, deliver behavioral interventions and voice training exercises on video

platforms [79]. Some part of the post treatment care of head and neck cancer patients can be conducted through telehealth platforms. Remote consultations are used to monitor recovery, manage side effects, and screen for recurrence symptoms. Patients report symptoms such as pain, dysphagia or voice changes that can lead to timely diagnostic imaging or endoscopic examination. Tele-oncology also helps in getting second opinion, conducting multidisciplinary tumor boards, and genetic counseling, particularly for patients with poor mobility or those who cannot reach academic centers. Telemedicine in pediatric otolaryngology is used in the management of conditions such as otitis media, adenoid hypertrophy, allergic rhinitis and epistaxis. Remote guidance for caregivers along with shared multimedia files helps in early intervention and enhances parental education [80].

Preoperative counseling and postoperative follow-ups are done extensively on virtual platforms. ENT procedures such as tonsillectomy, septoplasty, tympanoplasty, and endoscopic sinus surgery need patient education before surgery. These sessions can be done virtually to save clinic time and enhance patient understanding. Telehealth provides wound checks, medication management, symptom monitoring, and complication screening following surgery. This reduces the need for clinic visits and also enables early intervention when the need arises [81].

Patients with tinnitus and sensorineural hearing loss can get better management through remote counseling, sound therapy, and cognitive behavioral strategies provided through tele-audiology platforms. Patients can use mobile applications at home that integrate personalized soundscapes and guided mindfulness sessions [82]. Hearing aid users gain remote programming and troubleshooting services which decreases the need to travel frequently for older adults. Remote firmware updates and automatic hearing aid parameter adjustments based on environmental sounds are enabled by advanced systems [83,83].

6. Conclusions

The research explored clinical evaluation procedures across different medical products through an evaluation of telemedicine technologies together with drug and medical device and combined drug-device regulatory requirements. The regulatory framework analysis demonstrated that clinical trial methods for product categories vary through their framework rules and trial methodologies and risk assessments and approval processes. The distinction between clinical and regulatory approaches is essential for medical innovation today because hybrid therapies and integrated devices breach traditional rules.

Medical products require strict multi-stage trials with specific phases to test pharmacokinetics and safety and efficacy through extensive patient populations with controlled placebo-based studies. The risk classification system for medical devices supports adaptable clinical trials which evaluate performance and usability and device safety. The regulatory oversight for combined drug-device products creates extended difficulties in trial execution as well as manufacturing requirements and post-market monitoring procedures. The correct identification of product type during development ensures both simpler regulatory approval procedures and better clinical trial design and improved patient protection.

The telemedicine clinical study evaluated the clinical validity of a video-otoscopic telemedical device by examining its real-world applicability in medical practice. The study revealed a diagnostic agreement rate of 76.7% that demonstrates strong potential of the telemedicine system for remote otorhinolaryngology diagnosis. The study results indicated that therapy matching was lower at 59.2% because remote care settings presented difficulties in aligning diagnostic outputs with treatment choices. The research demonstrated that common medical diagnoses achieved better agreement levels yet rare and intricate cases created measurement fluctuations which required ongoing development of telemedical decision-support systems.

Telemedicine tools proved useful in clinical decision-making because substantial clinical concordance existed even when direct matches were absent. The research demonstrates both benefits and weaknesses of existing telemedical solutions which indicates the necessity for developing platforms that merge diagnostic tools with therapeutic functions to handle different clinical situations.

This thesis combines regulatory aspects with clinical trial data analysis to present a complete overview of medical product development and telemedicine implementation. The thesis demonstrates that healthcare innovation requires both technological advancement alongside strict clinical validation and regulatory clarity. Telemedicine expansion requires understanding its clinical performance and regulatory standards to create safe and accessible healthcare solutions that work effectively.

This study establishes essential connections between clinical research protocols and regulatory standards which provides crucial direction to developers researchers and clinicians who work within advanced medical product development. The paper demonstrates that accurate classification techniques combined with strategic trial planning and continuous clinical monitoring enable the efficient and safe delivery of innovative telemedical and combined drug-device products to patients.

7. Acknowledgements

First of all, I would like to express my gratitude and thanks to my supervisors, Professor Lajos Kemény, Professor Ildikó Csóka, for continuous guiding, encouraging, and supporting my work. I would like to thank László Szakács for providing me the opportunity to perform my scientific work at the Department of Oto-Rhino- Laryngology and Head- Neck Surgery. I would like to express my special appreciation and thanks to dr. Bence Sipos and dr. Gábor Katona for supporting me and sharing they expertise on drug and medical device development. Thanks to all of my colleagues at the Department of Dermatology and Allergology – Department of Oto-Rhino- Laryngology and Head- Neck Surgery and the Faculty of Pharmacy. Last but not least, I have many thanks to my family for their continuous encouragement, support, and background that enable me to create this work.

8. References

1. Schuhmacher, A.; Gassmann, O.; Bieniok, D.; Hinder, M.; Hartl, D. Open Innovation: A Paradigm Shift in Pharma R&D? *Drug Discovery Today* **2022**, *27*, 2395–2405, doi:10.1016/j.drudis.2022.05.018.
2. Park, J.J.H.; Mogg, R.; Smith, G.E.; Nakimuli-Mpungu, E.; Jehan, F.; Rayner, C.R.; Condo, J.; Decloedt, E.H.; Nachega, J.B.; Reis, G.; et al. How COVID-19 Has Fundamentally Changed Clinical Research in Global Health. *The Lancet Global Health* **2021**, *9*, e711–e720, doi:10.1016/S2214-109X(20)30542-8.
3. Aday, J.S.; Heifets, B.D.; Pratscher, S.D.; Bradley, E.; Rosen, R.; Woolley, J.D. Great Expectations: Recommendations for Improving the Methodological Rigor of Psychedelic Clinical Trials. *Psychopharmacology* **2022**, *239*, 1989–2010, doi:10.1007/s00213-022-06123-7.
4. Kasoju, N.; Remya, N.S.; Sasi, R.; Sujesh, S.; Soman, B.; Kesavadas, C.; Muraleedharan, C.V.; Varma, P.R.H.; Behari, S. Digital Health: Trends, Opportunities and Challenges in Medical Devices, Pharma and Bio-Technology. *CSIT* **2023**, *11*, 11–30, doi:10.1007/s40012-023-00380-3.
5. Flynn, R.; Plueschke, K.; Quinten, C.; Strassmann, V.; Duijnhoven, R.G.; Gordillo-Marañon, M.; Rueckbeil, M.; Cohet, C.; Kurz, X. Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What Was the Contribution of Real-World Evidence? *Clin Pharma and Therapeutics* **2022**, *111*, 90–97, doi:10.1002/cpt.2461.
6. Anawade, P.A.; Sharma, D.; Gahane, S. A Comprehensive Review on Exploring the Impact of Telemedicine on Healthcare Accessibility. *Cureus* **2024**, doi:10.7759/cureus.55996.
7. Singh, A.K.; Kasle, D.A.; Jiang, R.; Sukys, J.; Savoca, E.L.; Z. Lerner, M.; Kohli, N. A Review of Telemedicine Applications in Otorhinolaryngology: Considerations During the Coronavirus Disease of 2019 Pandemic. *The Laryngoscope* **2021**, *131*, 744–759, doi:10.1002/lary.29131.
8. European Parliament and Council. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC. Off. J. Eur. Union 2014, L158, 1–76.
9. European Parliament and Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. Off. J. Eur. Communities 2001, L121, 34–44.
10. International Council for Harmonisation (ICH). ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Current Step 4 Version, 9 November 2016.
11. Cagnazzo, C.; Cenna, R.; Basiricò, M.; Fagioli, F. EUROPEAN CLINICAL TRIALS REGULATION 536/2014: CONCERNS AND PERSPECTIVES OF A MEMBER STATE. *Ann Res Oncol* **2022**, *02*, 202, doi:10.48286/aro.2022.53.

12. Jørgensen, M.; Thomas, K.B.; Zerm, M.; Paarlberg, R.A. Protection of Personal Data and Commercially Confidential Information under the Clinical Trials Regulation (EU) No. 536/ 2014 – EMA "Revised CTIS Transparency Rules." *Med Writ* **2024**, *33*, 12–21, doi:10.56012/frkj6889.
13. Fneish, F.; Schaarschmidt, F.; Fortwengel, G. Improving Risk Assessment in Clinical Trials: Toward a Systematic Risk-Based Monitoring Approach. *Current Therapeutic Research* **2021**, *95*, 100643, doi:10.1016/j.curtheres.2021.100643.
14. Patrick-Brown, T.D.J.H.; Bourner, J.; Kali, S.; Trøseid, M.; Yazdanpanah, Y.; Olliaro, P.; Olsen, I.C. Experiences and Challenges with the New European Clinical Trials Regulation. *Trials* **2024**, *25*, 3, doi:10.1186/s13063-023-07869-x.
15. Yamada, O.; Chiu, S.-W.; Takata, M.; Abe, M.; Shoji, M.; Kyotani, E.; Endo, C.; Shimada, M.; Tamura, Y.; Yamaguchi, T. Clinical Trial Monitoring Effectiveness: Remote Risk-Based Monitoring versus on-Site Monitoring with 100% Source Data Verification. *Clinical Trials* **2021**, *18*, 158–167, doi:10.1177/1740774520971254.
16. De Mey, C.M. Phase I Studies in EU: Due Change in Compliance and Transparency under the EU Clinical Trials Regulation. *Eur J Clin Pharmacol* **2022**, *78*, 1047–1048, doi:10.1007/s00228-022-03293-3.
17. Westergren, T.; Narum, S.; Klemp, M. Biases in Reporting of Adverse Effects in Clinical Trials, and Potential Impact on Safety Assessments in Systematic Reviews and Therapy Guidelines. *Basic Clin Pharma Tox* **2022**, *131*, 465–473, doi:10.1111/bcpt.13791.
18. B, P.; Kothapalli, P.; Vasanthan, M. The Role of Quality Assurance in Clinical Trials: Safeguarding Data Integrity and Compliance. *Cureus* **2024**, doi:10.7759/cureus.67573.
19. Flores, L.E.; Frontera, W.R.; Andrasik, M.P.; Del Rio, C.; Mondríguez-González, A.; Price, S.A.; Krantz, E.M.; Pergam, S.A.; Silver, J.K. Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials. *JAMA Netw Open* **2021**, *4*, e2037640, doi:10.1001/jamanetworkopen.2020.37640.
20. De Jong, A.J.; Gardarsdottir, H.; Santa-Ana-Tellez, Y.; De Boer, A.; Zuidgeest, M.G. Experiences with Low-Intervention Clinical Trials—the New Category under the European Union Clinical Trials Regulation. *Clinical Trials* **2025**, 17407745241309293, doi:10.1177/17407745241309293.
21. International Council for Harmonisation (ICH). ICH Harmonised Guideline: Quality Risk Management Q9 (R1). Step 4 Version, 18 January 2023.
22. Fu, Z.; Liu, X.; Zhao, S.; Yuan, Y.; Jiang, M. Reducing Clinical Trial Monitoring Resources and Costs With Remote Monitoring: Retrospective Study Comparing On-Site Versus Hybrid Monitoring. *J Med Internet Res* **2023**, *25*, e42175, doi:10.2196/42175.
23. Yaqoob, I.; Salah, K.; Jayaraman, R.; Al-Hammadi, Y. Blockchain for Healthcare Data Management: Opportunities, Challenges, and Future Recommendations. *Neural Comput & Applic* **2022**, *34*, 11475–11490, doi:10.1007/s00521-020-05519-w.
24. Fields, B.G. Regulatory, Legal, and Ethical Considerations of Telemedicine. *Sleep Med Clin* **2020**, *15*, 409–416, doi:10.1016/j.jsmc.2020.06.004.
25. Andratschke, N.; Willmann, J.; Appelt, A.L.; Alyamani, N.; Balermpas, P.; Baumert, B.G.; Hurkmans, C.; Høyer, M.; Langendijk, J.A.; Kaidar-Person, O.; et al. European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer Consensus on Re-Irradiation: Definition, Reporting, and Clinical

Decision Making. *The Lancet Oncology* **2022**, *23*, e469–e478, doi:10.1016/S1470-2045(22)00447-8.
26. Qaderi, S.M.; Van Der Heijden, J.A.G.; Verhoeven, R.H.A.; De Wilt, J.H.W.; Custers, J.A.E.; Beets, G.L.; Belt, E.J.Th.; Berbée, M.; Beverdam, F.H.; Blankenburgh, R.; et al. Trajectories of Health-Related Quality of Life and Psychological Distress in Patients with Colorectal Cancer: A Population-Based Study. *European Journal of Cancer* **2021**, *158*, 144–155, doi:10.1016/j.ejca.2021.08.050.
27. Stans, J.; Verbandt, S.; Kromar, S.; Deleersnijder, A. Implementation of Regulation (EU) No 536/2014 as a Non-Commercial Sponsor: An Internal Survey and a Descriptive Analysis of Timelines. *Ther Innov Regul Sci* **2023**, *57*, 1113–1120, doi:10.1007/s43441-023-00553-x.
28. European Parliament and Council. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC. Off. J. Eur. Union 2017, L117, 1–175.
29. Council of the European Communities. Council Directive 93/42/EEC of 14 June 1993 Concerning Medical Devices. Off. J. Eur. Communities 1993, L169, 1–43.
30. Makeenko, M.; Chevallier, T. Post-Market Clinical Follow-up (PMCF) GAP Analysis for Legacy Devices Class III between the Medical Device Directive (MDD 93/42/EEC) and the Medical Device Regulation (MDR 2017/745): In Proceedings of the Proceedings of the 15th International Joint Conference on Biomedical Engineering Systems and Technologies; SCITEPRESS - Science and Technology Publications: Vienna, Austria, 2022; pp. 273–280.
31. Mohn, D.; Zehnder, M. Medical Device Regulation (MDR) from a Dental Perspective. *Front. Dent. Med* **2023**, *4*, 1155820, doi:10.3389/fdmed.2023.1155820.
32. Schmitz, A.A.; Font-Nieves, M.; Doucouré, T.; Podhaisky, H.-P. Impact of Rule 11 on the European Medical Software Landscape: Analysis of EUDAMED and Further Databases Three Years After MDR Implementation. *Ther Innov Regul Sci* **2025**, *59*, 365–378, doi:10.1007/s43441-025-00747-5.
33. Antal, A.; Ganho-Ávila, A.; Assecondi, S.; Barbour, T.; Bjekić, J.; Blumberger, D.M.; Bolognini, N.; Brunelin, J.; Chanes, L.; Dale, M.; et al. The Consequences of the New European Reclassification of Non-Invasive Brain Stimulation Devices and the Medical Device Regulations Pose an Existential Threat to Research and Treatment: An Invited Opinion Paper. *Clinical Neurophysiology* **2024**, *163*, 280–291, doi:10.1016/j.clinph.2024.03.039.
34. Beckers, R.; Kwade, Z.; Zanca, F. The EU Medical Device Regulation: Implications for Artificial Intelligence-Based Medical Device Software in Medical Physics. *Physica Medica* **2021**, *83*, 1–8, doi:10.1016/j.ejmp.2021.02.011.
35. Bretthauer, M.; Gerke, S.; Hassan, C.; Ahmad, O.F.; Mori, Y. The New European Medical Device Regulation: Balancing Innovation and Patient Safety. *Ann Intern Med* **2023**, *176*, 844–848, doi:10.7326/M23-0454.
36. European Parliament and Council. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on In Vitro Diagnostic Medical Devices

and Repealing Directive 98/79/EC and Commission Decision 2010/227/EU. Off. J. Eur. Union 2017, L117, 176–332.
37. Chiara, O. MDCG 2022-4 Rev.2: Guidance on Surveillance under MDR Article 120 for MDD/AIMDD Certified Devices; European Commission, Medical Device Coordination Group: Bilbao, Spain, 2024.
38. European Commission, Medical Device Coordination Group (MDCG). MDCG 2021-24: Guidance on Classification of Medical Devices; European Commission: Brussels, Belgium, 2021.
39. International Organization for Standardization (ISO). ISO 14971:2019—Medical Devices—Application of Risk Management to Medical Devices; ISO: Geneva, Switzerland, 2019.
40. European Commission, Medical Device Coordination Group (MDCG). MDCG 2019-16: Guidance on Clinical Evaluation (MDR); European Commission: Brussels, Belgium, 2019.
41. European Commission, Medical Device Coordination Group (MDCG). MDCG 2022-5: Guidance on Cybersecurity for Medical Devices; European Commission: Brussels, Belgium, 2022.
42. Ren, Z.; Bremer, A.A.; Pawlyk, A.C. Drug Development Research in Pregnant and Lactating Women. *American Journal of Obstetrics and Gynecology* **2021**, *225*, 33–42, doi:10.1016/j.ajog.2021.04.227.
43. Qouhafa, M.; Benaji, B.; Lebbar, S.; Soulaymani, A.; Nsiri, B.; El Yousfi Alaoui, M.H.; Abdelrhani, M.; Azougagh, M. Metric Identification and Mapping of Reimbursable Implant Codes in Morocco to the Global Nomenclature (GMDN) and European (EUDAMED) of Medical Devices. *Annales Pharmaceutiques Françaises* **2024**, *82*, 1025–1033, doi:10.1016/j.pharma.2024.05.005.
44. Friedman, L.M.; Furberg, C.; DeMets, D.L. Clinical Trials: A Methodologic Perspective, 4th Ed.; Wiley: Hoboken, NJ, USA, 2024.
45. Kumoluyi, R.; Khanolkar, A. Risk Management in Drug-Device Combination Product Development. *Ther Innov Regul Sci* **2022**, *56*, 685–688, doi:10.1007/s43441-022-00425-w.
46. European Medicines Agency (EMA). Guideline on Quality Documentation for Medicinal Products When Used with a Medical Device; EMA: Amsterdam, The Netherlands, 2022. Available Online: Https://Www.Ema.Europa.Eu/En/Documents/Scientific-Guideline/Guideline-Quality-Documentation-Medicinal-Products-When-Used-Medical-Device_en.Pdf (Accessed on 14 June 2025).
47. European Commission. EudraLex—Volume 4: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; European Commission: Brussels, Belgium, 2022.
48. International Organization for Standardization (ISO). ISO 13485:2016—Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes; ISO: Geneva, Switzerland, 2016.

49. Haleem, A.; Javaid, M.; Singh, R.P.; Suman, R. Telemedicine for Healthcare: Capabilities, Features, Barriers, and Applications. *Sensors International* **2021**, *2*, 100117, doi:10.1016/j.sintl.2021.100117.
50. Barbosa, W.; Zhou, K.; Waddell, E.; Myers, T.; Dorsey, E.R. Improving Access to Care: Telemedicine Across Medical Domains. *Annu. Rev. Public Health* **2021**, *42*, 463–481, doi:10.1146/annurev-publhealth-090519-093711.
51. Alenoghena, C.O.; Ohize, H.O.; Adejo, A.O.; Onumanyi, A.J.; Ohihoin, E.E.; Balarabe, A.I.; Okoh, S.A.; Kolo, E.; Alenoghena, B. Telemedicine: A Survey of Telecommunication Technologies, Developments, and Challenges. *JSAN* **2023**, *12*, 20, doi:10.3390/jsan12020020.
52. Ftouni, R.; AlJardali, B.; Hamdanieh, M.; Ftouni, L.; Salem, N. Challenges of Telemedicine during the COVID-19 Pandemic: A Systematic Review. *BMC Med Inform Decis Mak* **2022**, *22*, 207, doi:10.1186/s12911-022-01952-0.
53. Omboni, S.; Padwal, R.S.; Alessa, T.; Benczúr, B.; Green, B.B.; Hubbard, I.; Kario, K.; Khan, N.A.; Konradi, A.; Logan, A.G.; et al. The Worldwide Impact of Telemedicine during COVID-19: Current Evidence and Recommendations for the Future. *Connect Health* **2022**, *1*, 7–35, doi:10.20517/ch.2021.03.
54. Samarrai, R.; Riccardi, A.C.; Tessema, B.; Setzen, M.; Brown, S.M. Continuation of Telemedicine in Otolaryngology Post-COVID-19: Applications by Subspecialty. *American Journal of Otolaryngology* **2021**, *42*, 102928, doi:10.1016/j.amjoto.2021.102928.
55. Moentmann, M.R.; Miller, R.J.; Chung, M.T.; Yoo, G.H. Using Telemedicine to Facilitate Social Distancing in Otolaryngology: A Systematic Review. *J Telemed Telecare* **2023**, *29*, 331–348, doi:10.1177/1357633X20985391.
56. Lopez, A.M.; Lam, K.; Thota, R. Barriers and Facilitators to Telemedicine: Can You Hear Me Now? *Am Soc Clin Oncol Educ Book* **2021**, *41*, 25–36, doi:10.1200/EDBK_320827.
57. Drake, C.; Lian, T.; Cameron, B.; Medynskaya, K.; Bosworth, H.B.; Shah, K. Understanding Telemedicine's "New Normal": Variations in Telemedicine Use by Specialty Line and Patient Demographics. *Telemedicine and e-Health* **2022**, *28*, 51–59, doi:10.1089/tmj.2021.0041.
58. Ning, A.Y.; Cabrera, C.I.; D'Anza, B. Telemedicine in Otolaryngology: A Systematic Review of Image Quality, Diagnostic Concordance, and Patient and Provider Satisfaction. *Ann Otol Rhinol Laryngol* **2021**, *130*, 195–204, doi:10.1177/0003489420939590.
59. Daghighi, B.; Raee, V.M.; Kiah, M.L.M.; Tahaei, H. Privacy-Preserving Scheme Using Secure Group Communication for M-Healthcare Information Systems 2021.
60. Boateng, J.A. Patients' Satisfaction and Its Determinants in Outpatient and Inpatient Departments of Tertiary Hospitals in Ghana: A Literature Review. *TIJMG* **2019**, 149–160, doi:10.21522/TIJMG.2015.SE.19.01.Art015.
61. Murase, K.; Tanizawa, K.; Minami, T.; Matsumoto, T.; Tachikawa, R.; Takahashi, N.; Tsuda, T.; Toyama, Y.; Ohi, M.; Akahoshi, T.; et al. A Randomized Controlled Trial of Telemedicine for Long-Term Sleep Apnea Continuous Positive Airway Pressure

Management. *Ann Am Thorac Soc* **2020**, *17*, 329–337, doi:10.1513/AnnalsATS.201907-494OC.
62. Schoch, O.D.; Baty, F.; Boesch, M.; Benz, G.; Niedermann, J.; Brutsche, M.H. Telemedicine for Continuous Positive Airway Pressure in Sleep Apnea. A Randomized, Controlled Study. *Ann Am Thorac Soc* **2019**, *16*, 1550–1557, doi:10.1513/AnnalsATS.201901-013OC.
63. Fieux, M.; Duret, S.; Bawazeer, N.; Denoix, L.; Zaouche, S.; Tringali, S. Telemedicine for ENT: Effect on Quality of Care during Covid-19 Pandemic. *European Annals of Otorhinolaryngology, Head and Neck Diseases* **2020**, *137*, 257–261, doi:10.1016/j.anorl.2020.06.014.
64. Colbert, G.B.; Venegas-Vera, A.V.; Lerma, E.V. Utility of Telemedicine in the COVID-19 Era. *Rev. Cardiovasc. Med.* **2020**, *21*, 583, doi:10.31083/j.rcm.2020.04.188.
65. Portnoy, J.; Waller, M.; Elliott, T. Telemedicine in the Era of COVID-19. *The Journal of Allergy and Clinical Immunology: In Practice* **2020**, *8*, 1489–1491, doi:10.1016/j.jaip.2020.03.008.
66. McCool, R.R.; Davies, L. Where Does Telemedicine Fit into Otolaryngology? An Assessment of Telemedicine Eligibility among Otolaryngology Diagnoses. *Otolaryngol.--head neck surg.* **2018**, *158*, 641–644, doi:10.1177/0194599818757724.
67. Seim, N.B.; Philips, R.H.W.; Matrka, L.A.; Locklear, B.; Inman, M.; Moberly, A.C.; Essig, G.F. Developing a Synchronous Otolaryngology Telemedicine Clinic: Prospective Study to Assess Fidelity and Diagnostic Concordance. *The Laryngoscope* **2018**, *128*, 1068–1074, doi:10.1002/lary.26929.
68. Botrugno, C. Telemedicine in Daily Practice: Addressing Legal Challenges While Waiting for an EU Regulatory Framework. *Health Policy and Technology* **2018**, *7*, 131–136, doi:10.1016/j.hlpt.2018.04.003.
69. Gioia, G.; Salducci, M. Medical and Legal Aspects of Telemedicine in Ophthalmology. *Rom J Ophthalmol* **2019**, *63*, 197–207.
70. Parimbelli, E.; Bottalico, B.; Losiouk, E.; Tomasi, M.; Santosuosso, A.; Lanzola, G.; Quaglini, S.; Bellazzi, R. Trusting Telemedicine: A Discussion on Risks, Safety, Legal Implications and Liability of Involved Stakeholders. *International Journal of Medical Informatics* **2018**, *112*, 90–98, doi:10.1016/j.ijmedinf.2018.01.012.
71. Weinstein, R.S.; Krupinski, E.A.; Doarn, C.R. Clinical Examination Component of Telemedicine, Telehealth, mHealth, and Connected Health Medical Practices. *Medical Clinics of North America* **2018**, *102*, 533–544, doi:10.1016/j.mcna.2018.01.002.
72. Ravi, P.; Ramkumar, V.; Rajendran, A.; Saravanam, P.K.; Balasubramaniyan, S.; Nagarajan, R. Tele-Audiological Surveillance of Middle Ear Status among Individuals with Cleft Lip and/or Palate in Rural South India. *j am acad audiol* **2020**, *31*, 185–194, doi:10.3766/jaaa.18085.
73. Reeve, C.; Thomas, A.; Mossenson, A.; Reeve, D.; Davis, S. Evaluation of an Ear Health Pathway in Remote Communities: Improvements in Ear Health Access: Improvements in Ear Health Access. *Aust J Rural Health* **2014**, *22*, 127–132, doi:10.1111/ajr.12098.
74. Tötterman, M.; Jukarainen, S.; Sinkkonen, S.T.; Klockars, T. A Comparison of Four Digital Otoscopes in a Teleconsultation Setting. *The Laryngoscope* **2020**, *130*, 1572–1576, doi:10.1002/lary.28340.

75. Choi, J.S.; Yin, V.; Wu, F.; Bhatt, N.K.; O'Dell, K.; Johns, M. Utility of Telemedicine for Diagnosis and Management of Laryngology-Related Complaints during COVID -19. *The Laryngoscope* **2022**, *132*, 831–837, doi:10.1002/lary.29838.
76. Strohl, M.P.; Dwyer, C.D.; Ma, Y.; Rosen, C.A.; Schneider, S.L.; Young, V.N. Implementation of Telemedicine in a Laryngology Practice During the COVID-19 Pandemic: Lessons Learned, Experiences Shared. *Journal of Voice* **2022**, *36*, 396–402, doi:10.1016/j.jvoice.2020.06.017.
77. Boland, J.; Banks, S.; Krabbe, R.; Lawrence, S.; Murray, T.; Henning, T.; Vandenberg, M. A COVID-19-Era Rapid Review: Using Zoom and Skype for Qualitative Group Research. *Public Health Res Pract.* **2022**, *32*, doi:10.17061/phrp31232112.
78. Thai-Van, H.; Bakhos, D.; Bouccara, D.; Loundon, N.; Marx, M.; Mom, T.; Mosnier, I.; Roman, S.; Villerabel, C.; Vincent, C.; et al. Telemedicine in Audiology. Best Practice Recommendations from the French Society of Audiology (SFA) and the French Society of Otorhinolaryngology-Head and Neck Surgery (SFORL). *European Annals of Otorhinolaryngology, Head and Neck Diseases* **2021**, *138*, 363–375, doi:10.1016/j.anorl.2020.10.007.
79. Smith, J.D.; McConville, K.; Tiner, M.K.; Baldner, E.F.; Rosenberg, M.; Kupfer, R.A.; Hogikyan, N.D.; Morrison, R.J. Examining Use and Effectiveness of Teletherapy for Patients with Dysphonia. *Journal of Voice* **2023**, S0892199723000346, doi:10.1016/j.jvoice.2023.01.034.
80. Shirke, M.M.; Shaikh, S.A.; Harky, A. Implications of Telemedicine in Oncology during the COVID-19 Pandemic. *Acta Biomed* **2020**, *91*, e2020022, doi:10.23750/abm.v91i3.9849.
81. Chen, L.; Cheng, L.; Gao, W.; Chen, D.; Wang, C.; Ran, X. Telemedicine in Chronic Wound Management: Systematic Review And Meta-Analysis. *JMIR Mhealth Uhealth* **2020**, *8*, e15574, doi:10.2196/15574.
82. Guitton, M.J. Telemedicine in Tinnitus: Feasibility, Advantages, Limitations, and Perspectives. *ISRN Otolaryngology* **2013**, *2013*, 1–7, doi:10.1155/2013/218265.
83. Bush, M.L.; Thompson, R.; Irungu, C.; Ayugi, J. The Role of Telemedicine in Auditory Rehabilitation: A Systematic Review. *Otology & Neurotology* **2016**, *37*, 1466–1474, doi:10.1097/MAO.0000000000001236.