Publishable Summary for 16RPT03 InTENSE
Developing research capabilities for traceable intraocular pressure measurements

Overview

Measuring intraocular-pressure (IOP) with medical devices called tonometers is an effective way to screen for ocular hypertension - the only treatable risk factor for glaucoma, the leading cause of blindness. At the outset of the project, PTB was the only NMI with state-of-the-art capabilities in IOP metrology with many countries in Central Europe falling well behind. This knowledge was transferred to the consortium during the project and a competence centre for IOP metrology was successfully established at CMI. CMI has become a service provider to other Central European metrology institutes who, for lack of capacity or due to different priorities, can now refer their national customers to CMI. The project also initiated a European Centre for Medical Device Metrology (ECMDM) which will provide metrological support to a wider range of medical devices in the longer term.

Need

Screening for glaucoma, and the monitoring of disease progression, is undertaken using non-invasive IOP measurements, which are acquired with eye-tonometers. The correct performance of these devices is essential to ensure the correct diagnosis and treatment. Therefore, several European countries have national regulations for eye-tonometers to ensure their in-service performance. These regulations are implemented through periodic metrological checks or (re-)verifications by NMIs, DIs and/or by other authorised metrology bodies. At the outset of the project, few NMIs/DIs, had the capability to provide traceable calibrations for eye-tonometers and test devices. Furthermore, medical device metrology as a whole has been developed unevenly across Europe. For example, the EU's Medical Devices Directive (93/42/EEC) was introduced when the Eastern-European NMIs were in a transition period, hence, they were not able to catch up with current developments. The development of metrological research capabilities in the field of IOP, and possibly other ophthalmologic measurands, in Europe was therefore essential to ensure the proper operation of eye-tonometers, especially after they enter the market. The smart specialisation concept, which involved concentrating these developments at one location aimed to reduce duplication of effort and to make the most of available resources. In addition, it offers a significant advantage to international customers as they have a single point of contact where the relevant technical, legislative and regulatory information is available. Fast and efficient harmonised solutions can be offered.

Objectives

This project aimed to demonstrate the feasibility of the smart specialisation concept for medical device metrology in Europe using one medical device, eye tonometers for measuring IOP, in one region, Central Europe. The specific objectives of the project were:

1. To jointly develop traceable measurement and research capabilities at CMI for IOP measurements using common *contact* and *non-contact* tonometer types in the physiological and pathophysiological range of 10 mmHg – 80 mmHg.
2. To jointly develop research capabilities enabling CMI to identify other related ophthalmological measurands or non-standard measurement conditions, both existing and likely to be developed, and to evaluate them with respect to their suitability as targets for metrological checks.
3. To develop and implement a concept for smart specialisation in the field of traceable IOP measurements; for CMI to establish collaborations with the national and international medical research community and to develop a strategy for the perpetuation of the acquired research capability in IOP measurements and a strategy for offering calibration services from the established facilities to national

or international customers including NMIs/DIs; for other NMIs/DIs from within the consortium or other EURAMET countries to utilise these services, thus ensuring that a coordinated and optimised approach to the development of traceability in this field is developed.

4. To develop a strategic plan to extend the smart specialisation concept to other medical devices with a measuring function and beyond the Central European region.

5. To closely engage with all major regional stakeholders, including the responsible ministries, state authorities, calibration services and other governmental or non-governmental offices involved in ensuring that the legal metrological requirements in their countries are met, thus ascertaining that their needs are known and considered and that they know about the project and its results and accept and implement them for their future work.

Progress beyond the state of the art

At the beginning of the project, PTB was the only NMI with state-of-the-art capabilities in IOP metrology. This includes the calibrations that ensure traceability for today's standard tonometers as well as the research experience that is needed to adapt to the demands of new technological developments. In order to set up and establish a competence centre for IOP metrology (in Most, Czech Republic), CMI completed a series of advanced training sessions and successfully passed an external technical review and an external quality management audit. The centre provides calibration and verification services, in the field of IOP metrology, to international customers as well as training opportunities for European NMIs. By focusing this expertise and knowledge at one site, the project ensured that the existing (technical) state-of-the-art in IOP metrology is accessible to a broad range of countries through an efficient use of resources. This concept continues to be expanded by anchoring it to relevant international and European metrology institutions, and by making it sustainable, known and accessible to the widest metrological community. A strategic plan was developed to extend the smart specialisation concept to other European countries and to further medical devices, and the expansion of the centre at CMI continues with a focus on blood pressure measuring devices.

The state-of-the-art in ophthalmologic metrology was expanded as new ophthalmologic measurands were identified and assessed for their metrological relevance and potential. External scientific expertise from university partners (STU BA, UPOL) was crucial to achieve this goal. For the first time, mathematical modelling of the measurement process including the eyeball itself was introduced to this sector of metrology. Future decision making in the field of measurements of the additional ophthalmologic parameters can then be based on this rigorous scientific approach.

A virtual digital model of the eye's cornea was created by STU BA. Subsequently, a real mechanical model (artificial eye) was constructed, corresponding to the virtual model, for use in experimental verifications. Initial testing and verification of the artificial eye has shown very promising results. This is an essential step towards establishing a universal transfer standard in the field of IOP metrology. The artificial eye was also included as one of the transfer-standards in the IOP interlaboratory comparison between STU BA and CMI. This bilateral comparison confirmed the state-of-the-art measurement capabilities of CMI and STU BA.

Results

1. *To jointly develop traceable measurement and research capabilities at CMI for IOP measurements using common contact and non-contact tonometer types in the physiological and pathophysiological range of 10 mmHg – 80 mmHg.*

CMI gained the necessary technical, regulatory and legislative knowledge to become an expert in the field of IOP metrology through a series of advanced training courses. The efficacy of this training was successfully assessed by an independent team of international technical experts at the end of 2018. In addition, an external audit of the tonometry-related sections of CMI's quality management system was successfully completed. This ensured the quality of the traceable measurement and research capabilities jointly developed at CMI for IOP measurements using common (applanation, impression and non-contact) tonometer types in the physiological and pathophysiological range of 10 – 80 mmHg. As a result, a competence centre for IOP metrology was set up by CMI in Most, Czech Republic. The centre acts both as a service provider in IOP metrology for international customers as well as a provider of training for European NMIs and DIs.

During the project, CMI, with support from PTB, developed new procedures for the certification of a new type of testing device, which is used for the verification of air-puff tonometers. They also developed the procedures used for these verifications. All of these procedures were developed in close cooperation with the manufacturer

and they will continue to be used for the subsequent periodical (re-) verifications, which are mandatory for the continued use of the devices in countries like the Czech Republic and Germany. Before this project, there was no procedure for the verification of rebound tonometers. Therefore, CMI developed a new procedure for this, however it has not yet been included in any of the national guidelines that are used by testing offices during the mandatory verifications of rebound tonometers. Therefore, it is still difficult for these devices to be verified and for them to be operational for longer than two years in countries with mandatory verifications. The introduction of these new procedures will rectify this situation (expected in 2021). In addition, a bilateral interlaboratory comparison, between CMI and STU BA, was organised to help in the development of calibration services for future ophthalmological instruments and to support the development of a universal test device for non-contact tonometers. During this interlaboratory comparison, the potential of the artificial model eye was tested in comparison with a set of silicone eyes that is commonly used in calibration and verification procedures.

Overall, this objectives was fully achieved, resulting in the establishment of the complete measurement, research and training capabilities for IOP at CMI which are ready to serve all European stakeholders.

2. *To jointly develop research capabilities enabling CMI to identify other related ophthalmological measurands or non-standard measurement conditions, both existing and likely to be developed, and to evaluate them with respect to their suitability as targets for metrological checks.*

An understanding of the technical aspects of tonometers is not sufficient to ensure their precise and correct functioning. It is equally important to understand the intraocular pressure and the factors that influence it. Therefore, the most significant influential factors were identified for the most commonly used tonometers (Goldmann applanation tonometer, non-contact tonometers and rebound tonometers). Two main types of factors were identified: anatomical and external factors. The biomedical properties of the cornea, such as its rigidity, thickness or hysteresis, affect the IOP values measured by non-contact and rebound tonometers. Thus, in order to properly determine the IOP using these types of tonometers, the above-mentioned corneal properties need to be within normal limits. The effects of short term physiological stress factors on IOP were studied and it was shown that these factors can affect IOP values and significantly distort the results. Clinical studies were performed that focused on the influence of hypoxia, and head and body position on IOP values [1-3]. From a clinical point of view, the most relevant factors are a change of head and body position and short-term physical activity, which induce immediate clinically significant IOP changes. The supine position gave higher IOP readings on average than the sitting position, which is relevant when working with patients that are unable to sit or stand up. The other factors that were investigated, including short-term hypoxia and maximal activity, caused clinically insignificant mean changes of IOP, although individual fluctuations may exceed the safe range and may be a risk factor especially for glaucoma patients. The effects of these physiological stress factors disappear a short time after their termination, usually within 20 min. Based on these results, we recommend a rest of at least 20 min before the IOP measurement. The final reports also showed that coffee, energy drinks and water intake can change the IOP. Thus, we recommend avoiding drinking coffee or energy drinks on day of the measurement and drinking high amounts of water at least one hour before the measurement. The strong cooperation between the NMIs and the universities initiated during this study will continue beyond the end of this project.

At present, calibration and verification procedures do not account of all short term physiological stress factors. A physical artificial eye model was created by STU BA so that the virtual model of the human eye cornea can be validated. The physical artificial eye model has been further developed into a reference that could be capable of mimicking the real human eye during the testing or calibration of non-contact eye tonometers. Multiple prototypes were created, based on the initial design, in order to prepare a reliable, traceable and metrologically characterised reference device that will bring much needed metrology into the field of non-contact eye tonometry. The key material properties of the artificial cornea are currently undergoing complex characterisation in order to deliver the best possible measurement repeatability and to enable a full definition of the uncertainty budget. The potential of the artificial eye, for use in calibrations and verifications, was tested against classical test devices in an inter-laboratory comparison.

Based on these investigations, the necessary metrological checks will subsequently be developed for the emerging ophthalmological measurands (i.e. corneal thickness, corneal stiffness, etc.) which appear as additional functions in most modern eye tonometers, as well as for the instruments. This also enables CMI to undertake IOP measurements under non-standard conditions (e.g. incumbent patients).

Overall, this objective was fully achieved by the establishment of cooperation between CMI, UPOL, STU BA and SMU, which enables CMI to address the new ophthalmological measurands from the point of view of

metrological traceability. The key factors for this are both the virtual and artificial (mechanical) models of the eye which have shown satisfactory mutual agreement so far.

3. *To develop and implement a concept for smart specialisation in the field of traceable IOP measurements; for CMI to establish collaborations with the national and international medical research community and to develop a strategy for the perpetuation of the acquired research capability in IOP measurements and a strategy for offering calibration services from the established facilities to national or international customers including NMIs/DIs; for other NMIs/DIs from within the consortium or other EURAMET countries to utilise these services, thus ensuring that a coordinated and optimised approach to the development of traceability in this field is developed.*

In order to develop a smart specialisation concept in the field of IOP metrology, with relevant stakeholders in mind, the consortium organised three international workshops (in Bratislava, Warsaw and Berlin) with attendees from fifteen European countries. The attendees were from legislative and regulatory institutions, industry, metrology organisations and hospitals. During these workshops, the overall strategy being developed for smart specialisation in the field of IOP metrology was discussed and when necessary it was adapted to suit the needs of the stakeholders with consideration of European and national legislation and NMI level requirements.

By establishing the IOP metrology centre at CMI, the metrological and research capabilities developed during the project were made available to all NMIs/DIs in Europe and to international customers, including industry, testing and verification institutions, academia and research. The first services provided by the centre were focused towards manufacturers of eye tonometers, manufacturers of test devices for eye tonometers as well as test and calibration offices. These included advanced training on IOP metrology for both contact and non-contact tonometers, periodical calibrations and full traceability for most types of eye tonometers, certification of new test devices and testing procedures for the verification of new types of eye tonometers, and the organisation of interlaboratory comparisons in the field of the IOP metrology.

To ensure that the network on IOP metrology created during the project will continue to be in regular contact, a working group on eye tonometry was created including the consortium and active project stakeholders. This working group will be open to interested experts in the field of IOP metrology.

A white paper on the smart specialisation concept was developed to ensure that a coordinated and optimised Central European approach towards IOP metrology was created. It was made publicly available via the project's website. Besides offering an in-depth overview on the current situation in the field of IOP metrology, the paper presents the detailed services provided by the IOP metrology centre to all interested customers.

Overall, this objectives was fully achieved by creating a smart specialisation concept in IOP metrology and building a hub at CMI that can serve other nodes in this smart specialisation. This concept was widely promoted and is open to all NMIs/DIs and other IOP-measurement-stakeholders in Europe.

4. *To develop a strategic plan to extend the smart specialisation concept to other medical devices with a measuring function and beyond the Central European region.*

The current metrological approach can only be harmonised by enabling all European countries to work together, to develop common requirements and to provide all interested parties with access to expertise at the most advanced technical level. Therefore, the consortium developed a strategy focused on the establishment of a European Centre for Medical Device Metrology (ECMDM). Its main role will be to ensure a coordinated approach to metrology of the medical devices with a measuring function and it will have a double function both as a provider and as an advisor for interested NMIs and stakeholders. The centre will provide basic and advanced training and it will facilitate access to reliable services at the highest metrological level for all relevant parties from NMIs to manufacturers, test and calibration offices, as well as to members of the medical community.

It was essential from the outset to ensure good collaboration with legislators and regulators in order to avoid any conflict between the strategy developed by the project and European and national regulations. It was also important to keep up to date with the new developments in the field. Therefore, individuals from responsible authorities were invited to the events organised during the project, and the partners attended relevant regulatory events organised at national level and joined relevant national committees in the field of medical devices. In addition, regular contact was maintained with the management of the project’s NMIs.

The centre for intraocular pressure metrology established at CMI in Most, Czech Republic, cemented the foundation of the ECMDM. The first steps towards broadening the cooperation network established in the field

of IOP metrology beyond the Central Europe region, and to other medical measuring instruments, were made by adding blood pressure instruments to the priority list of the competence centre. This included an expansion to other European countries (Portugal, Slovenia, Ireland and Bosnia and Herzegovina).

CMI and PTB are in advanced discussions concerning the planned establishment of a European Centre on Medical Device Metrology based in the Czech Republic. A legal contract between the two institutions is under development.

A white paper on the strategic plan for a pan-European centre on medical device metrology was prepared and made publicly available via project's website. The document presents a thorough overview of the legal context in the field of medical devices, concentrating on the discrepancies that led to the current problems and clear short mid- and long-term plans to resolve them.

Overall, this objective was fully achieved by creating and promoting a strategic plan for a European Centre on Medical Device Metrology.

Impact

To ensure the dissemination of results and a sustainable engagement between the consortium and stakeholders, the partners attended national and international scientific or regulatory oriented workshops and conferences, standardisation committee meetings and they made a series of scientific and non-scientific papers publicly available. In total, 4 peer-reviewed papers were published in international journals (listed in the next section), 13 papers in trade/professional journals and 9 presentations were made at conferences, including IEEE MeMeA in Istanbul, Turkey, in 2019. A workshop was run on IOP metrology and a training course was given. The new OIML Recommendation '*Ophthalmic instruments – non-contact tonometers*' has been created and entered a voting stage. All of these documents can be found on the web-site intense.cmi.cz which will continue to be regularly maintained and updated. The site will continue to be used as a communication platform between the consortium and stakeholders.

Impact on industrial and other user communities

The consortium started the process of reorganising the metrology landscape for IOP measurements in Central Europe by establishing a competence centre on IOP metrology at CMI. The centre creates impact as it offers a significant advantage to international customers who have a single point of contact, where all relevant technical, legislative and regulatory information is available. The well-developed metrological infrastructure provides them with clear guidance, and hence legal certainty, on how the requirements can be met. As the centre is available to all interested Europe institutions, the project ensures that all countries can benefit from IOP metrology services at the highest standards. Thus, ophthalmology professionals and their organisations can now rely on a clear compliance, a correct traceability chain, correct measurement results and validated methods. In addition, patients throughout Europe will, in a long term, benefit from the most up to date metrological traceability in eye-tonometry.

New procedures were developed for the certification of a new type of testing device, which is used for the verification of air-puff tonometers. In addition, the procedures used for these verifications were developed. All of these procedures were developed in close cooperation with the manufacturer and they will be of continued benefit as they will be used for the subsequent periodical (re-) verifications, which are mandatory for the continued use of the devices in countries like the Czech Republic and Germany.

A new procedure was developed to meet the need to verify rebound tonometers. However, this procedure is not yet included in the national guidelines that are used by testing offices during mandatory verifications. The expected uptake of this procedure will ensure that these medical devices can be verified and be in operation for longer than two years in countries with mandatory verifications.

Impact on the metrology and scientific communities

This project has raised the level of intraocular pressure measurements in east-central Europe to the state-of-the-art found in the western part of this region. The regional authorities will benefit from the re-established traceability chain, the higher level of regional cooperation and the wider experience and information exchange enabling them to reflect and even to lead this research area. As this project has built the research capacity, the primary stakeholder group can confidently rely on a sustainable metrological infrastructure which will be able to flexibly adapt to technological or regulatory changes in the future.

The competence and training centre for IOP metrology established by this project at CMI will continue to provide services to international customers after the end of the project. These services will be continuously improved and upgraded according to the advancement of the technology and it will ensure and maintain an up-to-date IOP-metrology infrastructure for all interested European NMIs and international stakeholders.

The mechanical eye model, prepared within the project, is used for the practical simulation of the influence of different geometrical and mechanical corneal factors. This is needed for the verification and specification of their relationship with IOP readings and to validate the numerical modelling of the IOP measurement process. It is also the first step on towards the development of a much needed universal IOP transfer standard. The cooperation between the consortium and various academic institutions established during the project will continue and will be open for others to join.

Impact on relevant standards

Before the start of the project, two standardisation documents existed: the OIML Recommendation 145 and the ISO standard ISO 8612, which specify the safety and performance requirements for eye tonometers. Only the OIML Recommendation 145, valid for impression and applanation tonometers, specifies the metrological requirements of the test equipment in detail. The ISO standard, ISO 8612, is in practice valid for air puff tonometers only, and it explains how to perform a clinical trial, however it has no detailed requirements on how to ensure the traceability of the measurement. Therefore, the consortium initiated procedures for creating a new Recommendation that specifies the metrological requirements for non-contact tonometers. Thus, in June 2018, PTB successfully applied for a new OIML Recommendation “Ophthalmic instruments, Non-contact tonometers” under TC 18 “Medical Measuring Instruments”. The group working on the new project is composed of seven participant members, three of which (Austria, Czech Republic and Germany) are in this consortium. Two other partners (Poland and Slovakia) are observer members of the project. The second working draft (2WD) was issued in January 2020 and sent for comments to all members of the project. The first committee draft (1 CD) was sent to BIML. Based on the comments and discussions during the project, the consortium expects the OIML Recommendation to be published no later than summer 2021. A document containing “Good practice guidelines for traceable IOP metrology for applanation and impression and non-contact tonometers” was also developed within this project. The good practice guidelines are publicly available via the InTENSE project website.

Longer-term economic, social and environmental impacts

The project established clear and transparent requirements and guidelines for metrological checks of tonometers and associated test equipment. It will help private test laboratories as well as the manufacturers of new and innovative tonometers or multi-purpose ophthalmologic measuring devices and it is expected to reduce development costs and to facilitate faster innovations in this technology segment. The improved acceptance of metrological checks for tonometers will also provide EU citizens with better, more reliable and less uncertain IOP measurements. As a result, screening for ocular hypertension will become more effective.

The longer-term confirmation of the artificial eye as a universal transfer standard will not only improve the diagnosis of IOP, but it will also have a significant economic impact. Operators of eye tonometers and testing offices will have a single device offering them the certainty of correct measurement. This is in contrast to the current situation where a different compatible device is available for each eye tonometer, which implies a significant financial commitment for the affected stakeholders.

List of publications

[1] Najmanová E, Pluháček F, Botek M, Krejčí J and Jarošová J (2019) Intraocular Pressure Response to Short-Term Extreme Normobaric Hypoxia Exposure. Frontiers in Endocrinology 9:785. https://doi.org/10.3389/fendo.2018.00785

[2] Pluháček F, Unzeitigová A, Marešová K and Rybář J (2019) Influence of cornea on intraocular pressure measurement by ICARE PRO and ORA. Česká a slovenská oftalmologie 75:111. http://www.cs-ophthalmology.cz/cs/journal/3/articles/117/dl/327

[3] Najmanová E, Pluháček F and Haklová M (2020) Intraocular pressure response affected by changing of sitting and supine positions. Acta Ophthalmologica 98:e368. http://dx.doi.org/10.1111/aos.14267

[4] Pražák D, Sedlák V, Sınır E and Pluháček F (2020) Changing the status of mmHg. Accreditation and Quality Assurance 25:81. https://doi.org/10.1007/s00769-019-01414-7

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Internal Funded Partners: 1. CMI, Czech Republic 2. BEV-PTP, Austria 3. GUM, Poland 4. PTB, Germany 5. SMU, Slovakia 6. TUBITAK, Turkey	External Funded Partners: 7. STU BA, Slovakia 8. UPOL, Czech Republic	Unfunded Partners:
RMG: -		