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1 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.

2 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.

3 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.

4 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.*

At the start of the project, PTB was the only NMI with the current state-of-the-art in IOP metrology. This refers not only to the calibration capabilities that ensure traceability for today's standard tonometers, but also to the research background that is needed to adapt to the demands of new technological developments. To reach the same level of competence and expertise, CMI completed a series of advanced training sessions conducted by experts from PTB. During these training sessions, CMI gained the necessary technical, regulatory and legislative knowledge and became an expert in the field of IOP metrology.

Entry level training, for two new CMI personnel, was given by experienced CMI personnel in October 2017. The advanced training courses, for all of the CMI personnel that are involved in intraocular pressure metrology, were given by several PTB experts. The scope of these four courses was discussed and decided upon by all partners considering the identified technological and societal needs. The first training session was dedicated to the traceability of impression and applanation tonometers, followed by a training session addressing the complex traceability of non-contact (air-puff) tonometers. In order to understand and address the needs of international customers, the third training was dedicated to legislative and regulatory aspects, both at EU level, as well as national level. In addition to theoretical aspects, this training included the practical development of a new verification procedure in the current legislative context. The last training session concentrated on more modern types of tonometers: rebound and contour tonometers.

The efficacy of the aforementioned training courses was assessed by two international technical experts, external to the consortium. They determined that the staff of CMI and their laboratory met all requirements necessary to pass the technical assessment. In addition, an external audit of the tonometry related sections of CMI's quality management system was successfully completed. It was focussed on the standard operating procedures for verifications (calibrations) and type approvals of both contact and non-contact eye tonometers in the laboratory of CMI at the regional inspectorate in Most. The auditor found them to be in conformity with the CMI quality manual and in the field of contact tonometry, also with the series of recommendations OIML R-145 (2015) Ophthalmic instruments – impression and applanation tonometers.

These actions ensured the qualification 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 established at CMI Most. The centre has the role of a service provider in the field of IOP metrology for international customers and it offers training opportunities for European NMIs and DIs. The scope of the training centre was steered by BEV-PTP, GUM and TUBITAK, reflecting the needs of their stakeholders.

During the project, CMI with support from PTB, developed new procedures for the certification of a new type of testing device used for the verification of an air-puff tonometer as well as the procedures used for these verifications. These procedures were developed in close cooperation with the manufacturer and will continue to be used for the subsequent periodical (re-) verifications, which are mandatory for devices to continue to be used in countries like the Czech Republic and Germany. CMI also developed a new procedure for the verification of rebound tonometers. Such verifications did not exist previously to these efforts and are not yet included in any of the national guidelines that are used by the testing offices during the mandatory verifications, making it difficult for such types of medical devices to be verified and therefore to be in operation for longer than two years in countries with mandatory verifications. The existence of these procedures, ensures that such undesirable situations will be avoided.

In an effort to work towards the development of calibration services for future ophthalmological instruments and to support the development of a universal test device for non-contact tonometers, a bilateral interlaboratory comparison between CMI and STU BA, with support of SMU, was organised towards the end of the project. During these measurements, the potential of an artificial model eye was tested in comparison to a set of silicone eyes, which is a common test device used in calibration and verification procedures. Both these transfer-standards were tested in relation to two laboratory eye tonometers - non-contact eye tonometers of

the NIDEK brand, type NT-2000, series I and III respectively, both of which met the clinical trial requirements in accordance with ISO 8612. The first comparison round took place in the Ružinov Hospital in Bratislava, Slovakia. The second comparison round took place at CMI, the Regional Inspectorate in Most. The results were compared with the highest permissible measurement errors for electronic non-contact eye tonometers. For both, the silicone eyes and the eye model, the errors were in accordance with the permissible errors, except in one case (eye model, 11 mmHg nominal pressure point). This bilateral comparison confirmed the high potential of the eye model and consolidates the plan for the successful development of a universal transfer standard in the near future.

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. The capabilities of this centre were successfully audited, proved by an intercomparison and the centre has already started to develop the new testing procedures.

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.*

To ensure the precise and correct functioning of tonometers, it is not sufficient to focus solely on their technical aspects. Understanding the intraocular pressure and the factors that influence it is equally important. The most significant influential factors were identified by CMI, STU BA and UPOL for the most commonly used tonometers (Goldmann applanation tonometer, non-contact tonometers and rebound tonometers). These factors can be divided into two groups. The first group includes those factors, which affect the interaction of the eye with the measuring device. The second group is connected to the properties of eye tissue, eye geometry, and to the patient's current state of health. The corneal properties which can affect the IOP measurement are corneal thickness, the geometrical parameters of the cornea (radius of the central corneal curvature, corneal astigmatism) and biomedical parameters such as hysteresis or rigidity. If the values of some of these parameters exceed the normal range, the IOP reading can be falsely higher or lower. It is also known that a number of physiological processes cause changes or fluctuations in IOP. Such changes can influence the IOP immediately before the measurement and thus the measured IOP can differ from the ordinary IOP of the measured subject. Thus, the interpretation of the measured value can be complicated by short-time IOP changes associated with the various physiological processes. Moreover changes, as well as short-time fluctuations in IOP, can be risk factors for the development and progression of glaucoma. Multiple typical representatives of both contact and non-contact IOP measurement methods were analysed and specific critical influential factors were determined, firstly by a literature search then by experimental investigation of selected key equipment.

Influence of cornea on IOP measurement by rebound and noncontact tonometers

UPOL used the ICARE PRO and ORA G3 as representative rebound and non-contact tonometers to study the effect of corneal properties (corneal hysteresis, central corneal thickness, mean central corneal radius, corneal astigmatism) and age on the IOP reading and its repeatability. UPOL also compared both tonometers together and with the known properties of the Goldman applanation tonometer (GAT). A mutual comparison of both instruments has shown that ICARE readings and Goldmann-correlated IOP did not differ significantly, whereas corneal-correlated IOP was significantly higher in comparison with the mean of the ICARE reading by approximately 1.1 mmHg ± 3.6 mmHg. In both cases, however a relatively high variability of differences between instruments was found in individual eyes. Due to this variability, the mutual interchangeability of the results from each piece of equipment is impossible.

Recent studies, including our results, indicate that the measurement of intraocular pressure using rebound (ICARE) and non-contact (ORA) tonometers is influenced by corneal hysteresis and corneal thickness. The observed influence of corneal thickness may indirectly reflect the effect of corneal rigidity. Thus, if some of these parameters are markedly out of the normal range, the IOP reading can be distorted. The values obtained by rebound and non-contact tonometers are not interchangeable. Therefore, e.g. upon observation of IOP changes over time, it is always necessary to use the same type of tonometer.

Effect of short-term physical activity on IOP

Previous studies have shown that short-time moderate aerobic exercise causes an IOP decrease during and immediately after the activity. Our previous findings, obtained under well-defined and controlled conditions, proved this decrease. The maximal reduction in IOP was 2.7 mmHg ± 2.0 mmHg and was obtained immediately after the exercise. This clinically significant decrease (i.e. > 2 mmHg) was followed by a gradual

increase to the initial IOP (baseline) in minute 20 after the completion of the exercise. The immediate decrease correlated with the baseline. The correlation was confirmed by most of the other studies. The magnitude of the IOP reduction increases with exercise intensity. The maximal workload, leading to exhaustion, did not show, however exactly defined IOP changes. The main effect is high interindividual variability of IOP, represented by an increase in the IOP standard deviation up to 1.7-fold of the baseline in the observed group of subjects – the maximal exercise influences different subjects differently. The high variability persisted up to minute 10 after exercise completion and in minute 20 it returned to the initial value.

Effect of hypoxia on IOP

Based on previous studies, it seemed that hypoxia affects the IOP. The results are, however, ambiguous. The high-altitude changes result in two important effects – a decrease in air pressure and a corresponding decrease in the partial pressure of the inspired oxygen. Recent studies mostly evaluated both factors together in the form of hypobaric hypoxia. Moreover, in the case of actual hiking, the climb to the given altitude was connected with the physical aerobic activity, which results in an IOP decrease, and/or changes of other physical parameters in the surrounding environment. Therefore, UPOL studied hypoxia under normal atmospheric pressure and under well-controlled conditions in a laboratory. UPOL found an increase in IOP in response to short-term (10 minutes) normobaric hypoxia (1.2 mmHg ± 1.9 mmHg at minute 4 and 0.9 mmHg ± 2.3 mmHg at minute 10 of hypoxia), which returned to the baseline 7 min after hypoxia. The increase was higher for subjects with a higher degree of induced oxygen desaturation. Although the average increase was clinically insignificant, clinicians should be aware that some patients who perform the activities connected with short-term hypoxia may run the risk of an unsafe increase in intraocular pressure. Hypoxic changes can also influence the accuracy of the IOP measurement.

Effect of position change on IOP

It is a known fact that IOP is significantly affected by body position. The majority of the studies refer to the higher IOP values seen in the supine position compared to the sitting or upright position. Such an increase in IOP, as well as its quick changes, can be a risk factor for development and progression of glaucoma. IOP is usually measured in the sitting position, however many patients are transported in the supine position. Thus, the interpretation of measured values can be complicated by short-time IOP changes associated with the body's reposition before measurement and it is therefore important to know the time response of IOP related to the position change. Recent studies have mostly focused on a comparison of IOP values in a different position, but have only rarely studied the longer-time response of IOP. UPOL focused on the assessment of the IOP time response to the change in body position from a sitting to a supine position and from a supine to a sitting position immediately and during 30 minutes of rest in each position in healthy subjects. UPOL observed an immediate increase in IOP as a response to both considered changes of body position (2.6 mmHg ± 2.4 mmHg after lying down and 2.1 mmHg ± 3.1 mmHg after sitting up) and the subsequent gradual decrease with time. The mean IOP was 1.41 mmHg ± 2.4 mmHg higher in the lying period than in the sitting period. Moreover, UPOL observed a gradual decrease of IOP during the entire experiment – the mean IOP in the final sitting position was significantly lower (2.5 mmHg ± 1.9 mmHg) than in the initial sitting position. Thus, the IOP significantly changed especially immediately after the position change. The immediate IOP changes, induced by body reposition, were higher than 2 mmHg and from a medical standpoint they were clinically significant. This effect should be considered when IOP is measured after the patient's reposition, i.e. there should be an adequate delay between the reposition and the measurement. Based on our results, to be sufficient the delay must be longer than 5 min. This situation can occur, for example, during 24-hr monitoring of IOP, where position changes can be a distracting factor. Moreover, if the patients are calm for a longer time before the measurement, the IOP value can be affected by a gradual decrease with time. If the IOP is measured after an extended rest period, there is a risk that the IOP reading will be falsely lower. This effect is stronger for those with higher IOP, e.g. for glaucoma patients.

Effect of drinks on IOP

The drinking of water, caffeine in the form of coffee, tea or energetic drinks can influence IOP values. It has been demonstrated that drinking water significantly increases IOP with the maximal effect being seen 10 (2.24 mmHg ± 0.31 mmHg) or 15 minutes after ingestion of 1000 ml or 14 ml per kg of body weight. IOP was maintained significantly (however not clinically, < 2 mmHg) higher than the baseline for at least 30 min or 45 min after water ingestion. The consumption of 180 mg of caffeine in a 200 ml beverage causes an increase compared to the baseline up to 3.6 mmHg ± 1.1 mmHg and 3.4 mmHg ± 1.0 mmHg in minute 60 after caffeine ingestion in the case of normal tension glaucoma subjects or subjects with eye hypertension. The significant increase still persists in minute 90. As such, patients are more sensitive, UPOL suspects, than normal healthy people who will represent a smaller IOP rising. In contrast, caffeine consumption in the form of an energy drink

caused a decrease in IOP in young healthy subjects which persists for up to 90 min. This mean decrease (up to 1.7 mmHg ± 1.9 mmHg) was below clinical significance, however the individual changes can be clinically significant. This effect can be due to a combination of caffeine and other ingredients, especially taurine. Thus, the consumption of water increases IOP, whereas the consumption of energy drinks with a combination of caffeine and taurine decreases IOP. Caffeine consumption seems to increase IOP especially in the case of glaucoma or eye hypertension patients.

Recommendations

Clinical studies focused on the influence of hypoxia, head and body position on the IOP values were performed [1-3]. From a clinical point of view, the most relevant factors are change of position and short-term physical activity, which induce immediate clinically significant IOP changes. The supine position indicated on average higher IOP readings than the sitting position, which is a relevant aspect when working with patients who are unable to sit or stand up. The other factors investigated, such as short-term hypoxia or maximal activity, cause 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 incidence of the discussed parameters is limited to a small-time interval after their termination, usually within 20 min. Based on these results, UPOL recommends at least 20 min rest before the IOP measurement. The final reports also showed that coffee and energy drinks as well as water intake can change IOP. Thus, the measured subjects should avoid drinking coffee or energy drinks in the day of the measurement or drinking higher amounts of water at least one hour before the measurement.

Modelling of the measurement process

A virtual digital model of the cornea of the eye was created by STU BA which utilised also know-how of UPOL. 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 basis. As a consequence of the need for the validation of the designed virtual model of the cornea of the human eye, a real mechanical model (artificial eye) corresponding to the virtual model was created by STU BA with support from SMU. The initial intention for the verification of the mathematical model evolved into the development of the initial device as a reference that could be capable of mimicking the real human eye for the purpose of testing or calibration of non-contact eye tonometers. Multiple prototypes of the initial design were created in order to create a reliable, traceable and metrologically characterized reference device that would bring a much needed metrological aspect into the field of non-contact eye tonometry. Currently the device is at the stage of complex characterisation of key material properties of the artificial cornea in order to deliver the best possible repeatability of measurements and to enable a full definition of the uncertainty budget. The potential of the artificial eye for calibrations and verifications was tested against the classical test devices in an inter-laboratory comparison between STU BA and CMI. This is an essential step in the direction of establishing a universal transfer standard in the field of IOP metrology.

Based on these investigations, CMI can approach the expert support of STU BA for developing the necessary metrological checks 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. Moreover, many IOP measurement influencing factors were studied in detailed with practical recommendations arising from them.

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 for the development of 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.

The result was a publicly available white paper on the smart specialisation concept developed by all of the NMIs in the consortium to ensure a coordinated and optimised Central European approach towards IOP metrology. Besides offering an in-depth overview of 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.

Eye tonometers are instruments classified by EU law as medical devices with a measuring function (MDMF). The Medical Device Directive (MDD) and its successor, the Medical Device Regulation (MDR) were developed in order to harmonise the requirements for medical devices in the EU region. This was achieved for certain aspects in the cycle of a medical device, however issues arise for MDMF, both during the introduction of the devices on the market as well as during market surveillance.

In contrast to measuring instruments covered by the Measuring Instruments Directive (MID) or the Non-Automatic Weighing Instruments Directive (NAWID), the technical requirements for MDMF entering the market are minimal and vaguely formulated. This implies that each country, each notified body (NB) and each auditor can decide subjectively which technical requirements suffice for a MDMF to be able to enter the market. For eye tonometers the situation is even more inadequate, as the only ISO standard on the topic of eye tonometers (ISO 8612:2009) does not include technical requirements for these devices. Furthermore, certain aspects of market surveillance (e.g. verification of MDMF in operation) are left at the discretion of the individual countries. In response, certain countries developed national laws and by-laws that regulate such unclear aspects and define additional requirements for MDMF in operation (in the form of periodical mandatory metrological checks of such devices), thus leading to an unsatisfying, heterogeneous situation and an unclear context for manufacturers, calibration offices and operators of MDMF.

The NMIs in the consortium worked towards finding a solution to this unsatisfactory situation, surveyed national legislation concerning the MDMFs in use, and produced a smart specialisation concept meant to contribute to an increase in the harmonisation in the field of metrological checks of tonometers. The consortium brought together three groups of countries.

Germany and the *Czech Republic* have introduced periodical mandatory metrological checks for tonometers as well as having adopted national laws specifying technical metrological requirements based on which metrological checks are performed. The national metrology institutes (NMIs) of Germany (PTB) and the Czech Republic (CMI) have long-lasting experience in the field of the tonometry and are able to ensure measurement traceability and technical consultancy for their countries.

Austria and *Turkey* have introduced periodical mandatory metrological checks for tonometers however they have not adopted national laws specifying technical metrology requirements. Therefore, as a reference point, they indicate international standards, manufacturer specifications and state-of-the-art regulations.

Slovakia and *Poland* have not introduced periodical mandatory metrological checks nor have they adopted national laws specifying technical metrological requirements. In Poland, metrological checks of tonometers should be performed when necessary as foreseen in the technical specifications (manuals) issued by the manufacturers. Metrological checks should be performed by registered, competent entities authorised by the manufacturer (e.g. customer services). In Slovakia, the possibility of introducing metrological controls for tonometers is currently under examination.

As a first step towards the harmonisation of the currently heterogeneous metrological context, an IOP metrology centre was established at CMI with assistance from all NMI partners. By establishing this centre, the metrological and research capabilities developed during the project are being made available to all NMIs/DIs in Europe as well as for international customers, including industry, testing and verification institutions, academia and research. By condensing the expertise and knowledge at one site, it is ensured that the existing (technical) state-of-the-art in IOP metrology is being made accessible to a broad range of countries and at the same time the duplication of efforts and the waste of resources are reduced. The first services provided by the centre were focused towards manufacturers of eye tonometers and test devices for eye tonometers as well as test and calibration offices:

- a central hub for an information exchange network in this field,
- advanced training courses on IOP metrology for both contact and non-contact tonometers at the CMI laboratory in Most, Czech Republic,
- periodical calibrations and full traceability for most types of eye tonometers (it is not expected that the hub located at CMI would offer the regular verifications and/or calibrations of medical devices to the end users outside the Czech Republic. This is left to the governmental or private test laboratories in the individual countries. The creation of the advanced laboratories at other NMIs is encouraged. The hub at CMI will share its know-how with other nodes in such cases. However, regardless of whether a new traceability source appears or not, the CMI commits to keep the instrumentation and expertise to serve as the source of traceability in IOP metrology in the long-term.),
- certification of new test devices and testing procedures for new types of eye tonometers,
- organisation of the interlaboratory comparisons in the field of the IOP metrology,
- providing expertise and/or research in the field of the new measurands.

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 with members of the consortium as well as active stakeholders of the project. This working group will be open to interested experts in the field of IOP metrology.

Overall, this objectives was fully achieved by analysis of the relevant legislative framework in European countries, 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.*

In order to develop a strategic plan for extending the smart specialisation concept in IOP measurements to other medical devices with a measuring function (e.g. sphygmomanometers, ergometers, medical thermometers) and beyond the Central European region, the consortium followed several strategic steps.
First, the smart specialisation concept in IOP metrology was embedded in the existing metrological landscape. This was realised by initiating a new cooperation under the framework of OIML. As part of this cooperation, a new OIML recommendation “Ophthalmic instruments - non-contact tonometers”, complementing the existing OIML R 145 recommendation on applanation and impression tonometers was developed by PTB, with assistance of CMI and GUM. During its development several international NMIs, internal and external to the consortium took part, thus supporting the geographical expansion of the IOP metrology network created initially by the consortium not only beyond Central Europe, but beyond Europe. The Recommendation is currently in the Committee Draft stage.

Subsequent to the current project, CMI initiated a small collaborative project together with emerging countries in the field of IOP metrology in order to promote their fast development in this field.

An essential step in the development of the strategic plan was ensuring the conformity to the legal framework. In this scope, a close analysis of the latest developments with respect to the new legal context in the field of medical devices was performed during the project. The consortium identified an unsatisfactory legal state at EU level. MDR demands a coordinated approach towards market surveillance. However, contrary to this specific request, no coordinated European approach exists concerning the metrological verification of MDMF as part of market surveillance. This undermines the manufacturers’ free access to the market. Furthermore, no established procedure exists to ensure that the metrological requirements imposed by Notified Bodies during the conformity assessment, (when devices are placed on the market), and those imposed by NMIs for metrological checks (as part of market surveillance) are identical or compatible. This undermines the expectation of citizens and device manufacturers that EU legislation is consistent and uniformly applicable.

A harmonisation of the current metrological context can only be reached by offering all European countries the possibility to work together, develop common requirements and provide all interested parties with access to expertise at the most advanced technical level. A strategic plan for a pan-European centre on medical device metrology was prepared by CMI, GUM, PTB and TUBITAK and made publicly available. The document presents a thorough overview of the legal context in the field of medical devices concentrating on the discrepancies leading to the current unsatisfactory situation in the field. A solution to this problem is presented

in the document, with clear short, mid- and long-term plans. Essential at this stage was a good collaboration with legislators and regulators in order to avoid a conflict between the strategy developed by the project and the European and national regulations and at the same time to keep up with the new developments in the field. For this purpose, members of the consortium invited the responsible authorities to the events organised during the project, attended relevant regulatory events organised at national level and joined several relevant national committees in the field of medical devices. In addition, regular contact with the management of the NMIs involved was sustained.

The strategy developed by the consortium focuses on the establishment of a European Centre for Medical Device Metrology (ECMDM). Its main role will be to ensure a coordinated approach to MDMF metrology; 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 members of the medical community.

The foundation of the ECMDM is represented by the established centre for intraocular pressure metrology at CMI's premises in Most. This centre has been successfully offering training and metrological services (e.g. periodical calibrations, full traceability for most types of eye tonometers, certification of new test devices and testing procedures for new types of eye tonometers) to other European NMIs and their customers (mainly manufacturers of eye tonometers and test devices for eye tonometers as well as test and calibration offices). 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 which also came with an expansion to other European countries (Portugal, Slovenia, Ireland and Bosnia and Herzegovina).

While in the short-term (first 5 years), the centre will offer services focused on intraocular pressure metrology and blood pressure metrology, the centre will continue to expand its expertise in the mid- to long-term (10-15 years) to other MDMF (e.g. audiometers, thermometers). The ECMDM will address those MDMFs which are relevant for market surveillance from a metrological point of view (in other words, the devices for which recalibration is relevant and meaningful) and their metrological requirements are predominantly defined by the MDR and not preceded by other EU regulations.

In the longer run, the centre will not only concentrate on the market surveillance aspects of medical devices but it will also address existing discrepancies between the requirements for the MDMFs entering the market and the requirements for those in use. This way, synergic effects will be achieved by coordinating the conformity assessments and corresponding aspects of market surveillance. In this spirit, CMI initiated the process to become a Notified Body under the MDR and it is estimated that formal accreditation will be achieved by the end of 2022.

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

5 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.

6 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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