ABSTRACT

The adoption of shared procedures for performance assessment of devices and establishment of a consensus in standards can stimulate the deployment of novel Biophotonic techniques for clinical use by increasing the reliability and reproducibility of results.

To this aim, this workshop, promoted by the Photonics unit of the European Commission, has brought together different actors (researchers, clinicians/end users, companies, associations, standardization bodies, European Commission) to discuss their experiences and methodologies pursued in recent years within the framework of different EU projects, and other endeavors, as well as current actions and strategies in this field.

The associated challenges and opportunities were discussed, to enable a future common strategy and shared vision to be developed for improving the quality and effectiveness of Biophotonics devices, and therefore EU competitiveness. This meeting has therefore provided a platform for these key players to express the requirements from their respective areas of expertise for standardization and performance assessment in Biophotonics, the outcomes of which are summarised in this report.
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Challenges and Opportunities in standardization

OUTCOMES FROM WORLD CAFÉ DISCUSSIONS

Diffuse optics

Fluorescence

Mammography

OCT & Ophthalmology

Cerebral Oximetry
AIMS OF THIS WORKSHOP

- Share knowledge on what is going on in Europe and internationally in the field
- Provide various viewpoints on the topic (e.g. developers’ perspective, end users’ perspective)
- Define goals (i.e. when and how standardization is useful)
- Start to elaborate a possible common EU strategy, with coordination of different actors

BACKGROUND

Introduction

Novel technologies are being developed in Biophotonics, with a predominant focus in assisting in diagnostics and therapeutic treatment of patients with major diseases.

Biophotonics is a rapidly emerging field, with annual market growth close to 10% and a market share from European companies of around 28%, however this recent progress needs to be sustained and accelerated through EU support.

In FP7 nearly €100 million were spent on Biophotonics and Horizon 2020 so far has spent €85.6 million. There will be future calls for funding in the area. E.g. in 2019 two calls are focused on diagnostics and treatment: “Photonics devices to support monitoring therapeutic progress” and “Photonics systems for advanced imaging to support diagnostics driven therapy”.

Table 1. Summary of key Biophotonic techniques discussed during the workshop.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Diffuse Optical Imaging (DOI)</td>
<td>Probing the internal physiology and pathology of tissue using visible and near-infrared light, with contrast originating from intrinsic optical properties or extrinsic injected agents.</td>
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<tr>
<td>Photoacoustic (PA)</td>
<td>Measurement at the boundary of the acoustic signals generated by localized heating and pressure changes, which result from the absorption of injected light.</td>
</tr>
<tr>
<td>Raman Spectroscopy (RS)</td>
<td>Vibrational spectroscopy technique for monitoring biochemical composition of a biological sample based on tiny modifications in the spectra of inelastically scattered photons.</td>
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Optical Coherence Tomography (OCT) is a low-coherence interferometry technique producing 2D or 3D cross-sectional images of optical scattering.

Fluorescent Molecular Imaging (FMI) involves imaging the stokes shifted signal from auto-fluorescence or fluorescence agents engineered to target biomarkers specific to disease.

Successful translation of Biophotonic devices from benchtop investigations to commercially viable systems relies upon the reliability and the reproducibility of results. Additionally, their development requires an interdisciplinary approach, by bringing together communities from different backgrounds.

The performance of Biophotonic devices will inherently depend on several factors, including incorporated hardware and associated software, together with defined protocols for data acquisition and processing, all of which will depend upon the specific technique and clinical application. A summary outlining the key techniques discussed during this workshop is contained in Table 1.

Two approaches for assessing the performance of Biophotonic devices are commonly exercised, (1) phantom-based studies that provide a ground truth reference against which a device's performance can be validated, and (2) clinical trials involving a cohort of patients with known disease, using either in vivo subjects or in vitro samples, such that the diagnostic capabilities of the device can be compared to clinical outcomes.

In terms of composition, phantoms can be either solid (e.g. polyurethane plastic), or liquid (e.g. Intralipid, blood). The level of complexity of phantoms also varies. Examples include simple homogeneous phantoms, heterogeneous phantoms with multiple layers or an anomaly region, equivalent black volume phantoms, tunable / switchable phantoms, dynamic phantoms or hybrid phantoms, (e.g. to assess both optical and acoustic properties).

EXAMPLES OF CURRENT STATE OF THE ART

Diffuse optics

A SUMMARY OF THE EU EXPERIENCE OF THE WHOLE PROCESS IN DIFFUSE OPTICS, FROM CLINICAL PARADIGM TO INDUSTRIAL STANDARDS BY ANTONIO PIFFERI FROM POLITECNICO DI MILANO, ITALY.

Biophotonics plays a crucial role in healthcare, with advantages including chemical specificity, functional information, non-invasive, potentially non-contact, deep sensitivity within tissue, quantitative operator independence and production of scalable devices. These factors make Biophotonics unique from other modalities, but despite many good ideas in the laboratory, few of these reach the market.

The aims of standardization and performance assessment are to: anticipate technical issues, create benchmarks in research, facilitate deployment of industrial standards, mitigate market barriers,
facilitate use of open data to support machine learning by providing validated data sets, focus development of key clinical research, improve quality and reliability of clinical prototypes / trials, and finally improve patient health and reduce health costs with more reliable instruments.

It is intuitively preferable to start this process of standardization and performance assessment at a research level preceding any clinical trials, at which time the development is more tractable and less costly to alter.

The entire process in device development can typically take around 15 years and be separated into the following stages: (1) clinic to physics: where a clinical problem is translated into a physical model, for example a two layered model for brain imaging, (2) protocols: refine the parameters of devices through multicenter consensus, such as the BIP, MEDPHT and NEUROOPT protocols (3) phantoms: multicenter assessment comparing phantoms to establish which standard is best to use as a common reference, (4) lab comparison: multi-laboratory comparison in performance of devices, for example the assessment of the variability observed between cerebral oximeters, (5) instrument comparison in clinics: for example the SAFEBOOSC study, and finally (6) establishing industrial standards for the market acting as a quality control on patients health.

An example was given of the framework being exercised within the EU BITMAP project, with Action 1 to compare measurements between devices in different labs using the same phantom set, Action 2 to create cloud based open access datasets and Action 3 to compare data analysis methods using these datasets.

Biophotonics can learn from other fields, such as high energy physics. When an International discovery is found in this field, the finding is confirmed by many groups to allow progress. Even though the biological medium is highly complex, results still need to be confirmed in this way.

Ideas for a common EU strategy are to facilitate multi-laboratory comparative studies on protocols and with phantoms, to favor interactions among EU projects, and to establish stronger links with EU institutions and agencies.

Fluorescence Molecular Imaging

WORK ON STANDARDIZATION IN FMI BY DIMITRIS GORPAS FROM HELMHOLTZ ZENTRUM MÜNCHEN AND TECHNISCHE UNIVERSITÄT, GERMANY.

Fluorescent agents engineered to target pathophysiological features of diseases, such as ovarian cancer, can assist surgeons by offering a “red-flag” method to better identify suspicious areas. Interest in this technology from industry has led to the development of several systems for interoperative FMI guided interventions either with targeted or nonspecific fluorescence dyes.

Many aspects can impact the fluorescent signal strength and therefore performance, making it difficult to directly compare the outcomes of different clinical trials. These can include ambient lighting, system camera parameters, wavelengths measured, depth of fluorescence activity and the tissue optical properties.

FDA approval currently requires a specific system in combination with a corresponding specific agent. Showing complementary performance between systems through standardization should remove this codependency and therefore lead to an increase in approvals of clinical trials.
An example of the impact that standardization has on FMI was provided when testing newly developed tracers in pre-clinical settings the selection of appropriate imaging system is challenging as devices are not currently comparable.

Phantoms can play a number of functions in FMI, to allow the comparison between different systems performances, the configuration of optimal working conditions by adjusting system parameters, and can provide comprehensive information about these parameters over time to ensure repeatability. They can also serve as targets for quality control before each imaging session.

A multiparametric, composite phantom was presented, which was developed to test various imaging parameters. Referencing all data to a single phantom such as this should aid development of tracers and boost the clinical translation of this technology. The use of SI units was also encouraged, to make these comparisons traceable when developing new systems.

Future phantom designs will need to consider whether one single multispectral phantom is preferable or multiple different phantoms are needed for each wavelength, if targets should be exchangeable or fixed, and establish whether a 3D printable design can be used to reduce cost and increase reproducibility.

An example from which FMI can learn is coherent microscopy, in which the use of a standard test sample is advocated to standardize resolution claims.

The requirements of future standards for FMI will also need to consider specific applications, with the conditions for open surgery distinct from laparoscopy and endoscopy, both of which are internal imaging procedures and will require greater levels of standardization.

Working groups will be important for bringing together academia and industry, both at a national and international level. In the United States, work is being carried out on comparison of calibration and standardisation approaches for fluorescence guided imaging systems and benchtop fluorometers within the American Association of Physicists in Medicine and the FDA. Within Europe, the European society of molecular imaging (ESMI) are working on standardisation in FMI.

Photoacoustic Imaging

AN OVERVIEW AND INITIAL OUTCOMES FOR A NEW INTERNATIONAL STANDARDIZATION INITIATIVE IN PHOTOACOUSTIC IMAGING WAS PRESENTED BY JAMES JOSEPH FROM UNIVERSITY OF CAMBRIDGE, UK.

There is a strong desire for standardization within PA at the moment, as research moves into clinical trials. As a field in its relative infancy, standardization of PAI imaging systems and useful PA biomarkers such as total hemoglobin concentration, oxygen saturation of hemoglobin, dynamic contrast enhancement etc., which are indicative of diseases are needed.

A biomarker roadmap produced by Cancer UK, demonstrated that the first translational gap to overcome was to perform technological validation through multicenter studies, demonstrating their precision, repeatability and reproducibility.

Two types of phantoms will be required to achieve this in PAI, (1) biomimetic, tissue mimicking phantoms that can recapitulate precise optical and acoustic properties in a customizable way, to mimic the tissue and biomarkers of interest through tailoring the spectral properties and (2) physiological phantoms that recapitulate precise modulation of photoacoustic biomarkers.
Desirable characteristics of these phantoms are that they are composed of easy to buy or make materials, are easy to maintain, are durable long-term and can be recalibrated.

An international consortium was established, combining partners from both industry and academia. This involves five working groups, two focused on defining the optical and acoustic properties for phantoms, one focused on the PAI system configurations, one focused on the data format and finally one group focused on methodology and study design.

Expected outcomes from the consortium are the definition of reference wavelengths, a standardized recipe for the phantom which is proven to be reproducible for establishing precision, quality checking and quality control of PAI systems, define optimized systems parameters and specification frameworks and curated open access data. Resulting outcomes from this consortium are to be published in an open access journal.

NIRS Oximetry Devices Using Blood Phantoms

WORK USING BLOOD PHANTOMS TO ASSESS CEREBRAL OXIMETRY WAS PRESENTED BY MARTIN WOLF AT THE UNIVERSITY HOSPITAL OF ZÜRICH, SWITZERLAND.

In the context of cerebral oximetry, motivations behind standardization were outlined as: (1) from a scientific point of view, to ensure values of oxygen saturation are accurate and resulting from signals sampling the brain and not superficial layers, and (2) to ensure that different brands provide the same values.

Guidelines are a high priority both for manufacturers, as they want to know how to best test a device to allow it to be commercialized, and for patients, as they are concerned that the instrument provides a reliable diagnosis and is safe to use.

Previously oximetry devices have been calibrated in vivo using blood samples from the jugular bulb. This approach has multiple flaws including being unethical, not suitable for neonates, measures brain oxygenation whilst an oximeter has superficial contributions, and is reflective of the entire brain whilst oximeters only have contributions from a small compartment. This lack of knowledge about compartment size being interrogated in oximeters means this must be assumed.

Together these factors result in a high disagreement between different brands of instruments with both a high inter-individual variability and systematic differences, creating particular issues when establishing alarm limits for clinical intervention.

A 3rd generation blood phantom was presented, which has been shown to be highly repeatable, for example during multiple cycles of oxygen variation which can be carried out in a single session. By varying the thickness of the superficial layers of the phantom, this can be used to represent either neonate or adult heads.

Results from a study comparing the performance of several different oximeter brands using this blood phantom demonstrated a highly linear response in measures of StO2 between most instruments, however the absolute recovered values did not agree, with a range of gradients and intercepts for these linear relationships. The publication from this work of conversion tables between instruments enables comparison between studies in the literature in which different devices are used.
More studies such as this comparing different systems performances are desirable in future and will be important to demonstrate value and prestige of a standard once established. Currently, the FDA is requiring the jugular bulb approach for new devices, however it was recommended that the blood phantom approach should be promoted into the norm within Europe and Asia.

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**Breast Imaging Optical Techniques**

**A SUMMARY OF PHANTOMS FOR EVALUATION OF LIGHT-BASED BREAST IMAGING TECHNOLOGIES WAS PRESENTED BY SRIRANG MANOHAR FROM UNIVERSITY OF TWENTE, THE NETHERLANDS.**

The Smart Optical and Ultrasound Diagnostics of Breast Cancer (SOLUS) project aims to develop a multimodal hand-held probe system, combining ultrasound (US), shear-wave elastography and diffuse optics to improve specificity when imaging the breast for *in vivo* cancer diagnosis.

The system is very complex so requires a complex phantom for performance evaluation that can interact with the imaging modalities on all mediums. The SOLUS project looked at optical phantoms and investigated their intrinsic acoustic properties. It was reported that adjusting the absorption and scattering properties have a negligible impact on the speed of sound, resulting in the production of a phantom kit.

In the PAMMOPTH project, which looks at combining multiwavelength PA and US 3D imaging of the breast, an alternative complex 3D layered semi-anthropomorphic phantom was developed by taking a transparent acoustic phantom and tuning its optical properties.

It consisted of a base material made from PVCP, with layers to represent fat and fibroglandular tissue produced using 3D printed molds of a segmented breast MRI, and a skin layer make from silicone rubber. In future work, blood vessels and malignant tumors will be incorporated into this phantom.

In order to fully assess the system performance in PA you need a certain level of complexity in the phantoms, such as those presented, such that for example the curvature in the layers can mimic realistic internal reflection. As complex phantoms can be harder to reproduce however, the level of complexity needs to be carefully chosen to allow standardization.

It will be important to compare and validate the performance using these complex phantoms with other, individual imaging modalities and to develop more ideas on useful material compositions.

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**Raman Spectroscopy**

**COORDINATION AND STANDARDISATION ACTIVITIES IN RAMAN SPECTROSCOPY WERE PRESENTED BY THOMAS BOCKLITZ FROM THE LEIBNIZ INSTITUTE OF PHOTONIC TECHNOLOGY, GERMANY.**

RS can be applied to indirectly measure the chemical composition of a tissue, with applications in Biotechnology and cancer detection. RS combines experimental techniques to measure the spectra and computational techniques using machine learning to extract the relevant medical information.
The typical workflow in RS is, (1) identifying a task or question, (2) experimental design, (3) correction for artefacts and pre-processing, (4) spectrometer calibration and (5) analysis of the model using machine learning.

RS poses some unique challenges in terms of standardization, as it doesn’t typically solve one specific clinical question, so it will therefore be important to establish exactly where, when and how it will be useful to implement standardization in RS.

It is not possible to standardize the experimental protocol and sample preparation, as this depends on the specific sample and is based on experience in previous research.

Standardization may be useful in sample size planning, where the number of samples needed to gain significant results can be based on the learning curve.

Preprocessing steps which correct for artefacts or spikes depend on sample or devices, which can either enhance or diminish model accuracy.

The most critical part is the spectrometer calibration, in which the inherent fingerprint is accounted for. Difficulties in fully removing the influence of the spectrometer with published protocols means that currently all training of machine learning algorithms in RS are carried out on a single device and multicentre trials are not implemented. The community will need to work further on standardizing calibration and model transfer approaches for setup-independent spectra.

Work being carried out in Europe and internationally include wavenumber and intensity standardization within the VAMAS trial, and comparison of Raman spectra between labs in a European network called Raman4Clinics.

Metabolomics with MRI has similar issues in terms of fingerprinting from which Raman can learn. Industry will need to be engaged to overcome intellectual property issues to push for open data or knowledge of pre-processing steps.

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**Ophthalmology**

**Work on Phantoms and Standardisation in Ophthalmology was presented by Francesca Rossi from IFAC_CNR, Italy.**

Feedback to the speaker from clinical partners was that “There is no standard in ophthalmology, everything is in the surgeon’s hands.” Examples of where standards are needed include drug dosing in photo-mediated treatments, benchmarking the medical device in clinical settings, surgical training and for patient safety.

Phantoms in ophthalmology need to be transparent, easily fabricated, easy to handle and not expensive. The eye is highly complex, so nothing exists at the moment that can mimic the whole behaviour of the eye, however an existing commercially available phantom was presented that tests the resolution in OCT.

*Ex vivo* human or animal models are commonly used for testing a devices performance. Issues with this approach include the rapid degradation of *ex vivo* eyes, ethical issues using animal models and a difficulty in choosing the correct representative model, for example a difference in the layer thickness between animal and human eyes can lead to incorrect laser dosage for phototherapy.
Examples were presented of approaches to standardization including the development of a complex heterogenous eye phantom for ophthalmic surgery by Folgi et al., 3D-printing of human corneal stroma equivalent by Isaacson et al., and 3D printing phantoms of retinal photoreceptors cells for OCT evaluation by Kedia et al.

It was proposed that it would be beneficial to adopt a common EU strategy similar to that outlined by the FDAs Centre of Devices and Radiological Health (CDRH) in the document “A strategic roadmap for establishing new approaches to evaluate the safety of chemical and medical products in the United States”, which aims to reduce the burden on testing in animals. Key points from this roadmap are the convergence of the medical, research and industrial needs and clear communication between stakeholders.

MORE ACTORS IN DIFFERENT DOMAINS

Industry

WORK ON BUILDING A SMART MULTI-KET INDUSTRY DRIVEN MEDTECH VALUE CHAIN INCLUDING BIOPHOTONICS BY PAUL GALVIN FROM EMERGING SMART TECHNOLOGIES FOR HEALTHCARE (ESTHER), TYNDALL, IRELAND.

Three pillars seen from industry for innovative, advanced and integrated healthcare solutions are (1) to advance integrated global and medical solutions to serve the continuum of care, (2) to develop the full potential of digital health, and (3) leverage the fast development of key enabling technologies (KET).

There is an opportunity in Biophotonics for intervention at several stages on the continuum of care pathway (1) predictive studies in pre-acute care, (2) diagnosis and treatment in acute care, (3) education in post-acute and finally (4) homecare and wellness.

Standards are desired from industry to ensure high quality data, with patients’ needs at a central focus, and industry will need to be involved in order to link the value chains. It was suggested that the level of standards will need to vary within these different stages on the continuum of care, with the highest requirements expected from the acute stage.

ESTHER is a cross cutting initiative which brings together key players from all areas and aims to bridge the gaps between information technology and clinical procedures.

Medical devices have to date focused on precision engineering. The impact aims of the ESTHER initiative are to produce a value-based outcome after 5 years, 300 new start-ups at 10 years with added value to the healthcare system, 1000 innovative solutions for improved patient outcomes at 15 years, and stable or decreasing healthcare costs to GDP ratio at 20 years.

Standards are needed at many levels of the value chain, such as CE marking, regulatory approvals and HTA reimbursement, and it is important that they are understood at each level.

Research and development in Biophotonics must be informed by both patient and industry requirements by facilitating a close collaboration between clinician and contract developer. The challenge is how to best coordinate this with a patient centered approach and it was the speaker’s opinion that although stakeholders must be involved, a top down approach will not work.
Active discussions are currently taking place on a public private partnership on health with Horizon Europe, involving both stakeholders and members of the commission.

An example was given of a successful value-chain when technology has reduced the cost on the healthcare system, in which a solution for arthroscopy which reduces time for patient recovery has saved the taxpayer money.

A potential valley of death at the CE marking stage was identified, as this requires large financial resources.

It was highlighted in discussions that a lack of knowledge on the regulatory framework and legal aspects is often encountered within the academic community, particularly with biomedical devices, so during projects it will be important to educate and consider these factors from the beginning. This can be achieved by involving potential end users to overcome hurdles, which will be especially important as the relevant new EU regulations are approved.

Other issues to consider are the liability aspect, when involving human trials, and the human factors aspect, as production of an advanced prototype at a concept stage without considering the human factor is not beneficial.

From a clinician’s point of view, it was suggested that CE marking at a research level would be beneficial.

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**LESSONS FROM THE PAST, PRESENT PRACTICE & FUTURE NEEDS FOR STANDARDIZATION IN PHOTONIC MEDICAL DEVICES BY FOKKO WIERINGA, IMEC (ALSO ON BEHALF OF DUTCH KIDNEY & HEART FOUNDATIONS), THE NETHERLANDS.**

Disruptive technology cannot by definition be already included in the standards; however industry is needed to mass produce products and make it affordable to translate the technology into the clinic.

There are economic benefits from standardization as it is crucial for market access in a medical domain and therefore makes technologies profitable. Participating in standardization therefore boosts innovation.

An example of a single chip health patch used in immunotherapy for cancer was presented. By making a smaller and cheaper device with improved performance, this reduced blood refining time from 3 days to 1 hour, which was useful for medical professionals.

Sources of innovation include research institutes who make KETs, or key opinion leaders like clinicians who identify a technological need. These ideas need to be picked up by industry to be commercialized.

Bodies regulating standards include the International Commission on Non-Ionizing Radiation Protection (ICNIRP), the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Included within this the structure of international standards are basic standards, collateral standards, particular standards and standards on other topics. As an example, a general challenge in Biophotonics is poor signal to noise ratio of transmitted light, however signal strengths above a specific limit can burn tissue, so IEC 60601 provides a foundational layer of standards to prevent these hazards.

Example steps to bring technology to patients include: identify unmet needs, develop IP protection, build optical instrument, clinical trial, redesign prototype, repeat trial, manufacture and return on investment for society.
Obtaining government approval for market access is another valley of death to be avoided. Once market access has been acquired, healthcare providers still need to ensure reimbursement from the government or health insurance companies.

A number of standards already exist related to Biophotonics, including (1) surgical, cosmetic, therapeutic and diagnostic laser equipment, (2) surgical luminaires and luminaires for diagnosis, (3) infant phototherapy equipment, photodynamic therapy and photodynamic diagnosis equipment, (4) optical fibers and (5) photonic integrated circuits.

Standardization combined with road mapping can provide the best results, for example road mapping has made semiconductors available and affordable. A global integrated photonics roadmap has been devised by PhotonDelta involving many members. Roadmaps should always remain flexible.

The concept of coopetition was proposed, in which we work together when needed but compete to add unique value.

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International Regulatory Bodies

A REVIEW OF INTERNATIONAL ISO/IEC STANDARDIZATION IN FNIRS AND CEREBRAL TISSUE OXIMETRY BY HEIDRUN WABNITZ FROM PHYSIKALISCH-TECHNISCHE BUNDESANSTALT, GERMANY.

ISO, IEC and the International Telecommunication Union (ITU) are three international organizations involved in world standards cooperation.

The principles of these international standards are that only a single standard is established, that once established they have priority, that they should have worldwide acceptance and that they remain unchanged when adopted. Experience shows however that in practice there can sometimes be divergence, for example between CE and FDA.

International NIRS standards are dealt with in a joint working group called oximeters, with contributions from ISO relating to the anesthetic respiratory equipment aspects and from IEC for the electrical equipment in medical practice elements.

This has resulted in standards being established for: (1) pulse oximeters measuring oxygenation in the finger, (2) functional near infrared spectroscopy (IEC 80601-2-71:2015), in which attenuation changes over time due to functional brain activation, and (3) standards are currently being drafted for cerebral oximetry, which recovers absolute values for oxygen saturation (ISO 80601-2-85:2015).

A family of standards for medical electrical equipment already exists (IEC 60601), which address basic safety with any physical risks (mechanical, electrical, radiation etc.) and essential performance, related to the loss of clinical functionality which results in unacceptable risks in patients.

Functional (f)NIRS is not considered to have essential performance, as it is not related to diagnostic information with unacceptable risks in clinical outcomes.

Nevertheless, a performance test was still included in the fNIRS standard, using a turbid phantom simulating a change with a defined procedure including both the measurement and algorithm. This test has advantages as it is simple, easy to implement and attenuation changes are independent of wavelength. Some limits are that it does not test the linearity of devices, doesn't work for reflective geometries and simulates a larger change than typically observed.
In contrast, for cerebral tissue oximetry essential performance is important, as accuracy of recovered values is relevant to therapeutic decisions.

The traditional test widely used for oximetry performance is *in vivo* validation using controlled human desaturation, where oxygen saturation of inhaled air is decreased, whilst blood samples from the artery and jugular vein are measured as reference. An advantage of this approach is it includes inter-subject variability; however disadvantages are results are not quantitatively comparable between devices, there are ethical concerns and it can only be implemented on healthy adults.

The stages involved in establishing international standards are (1) new work item proposal, (2) working draft, (3) committee draft, (4) draft international standard, (5) final draft and (6) international standard published.

It is useful to have input from research experts in standards at an early stage, and the process should be industry driven as markets desire standardization.

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**Scientific Publishing**

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**A PERSPECTIVE ON KEEPING UP STANDARDS IN SCIENTIFIC PUBLISHING BY OLIVER GRAYDON FROM NATURE PHOTONICS, UK.**

Scientific publishing bodies, such as Nature Photonics, have a keen interest in maintaining standards to ensure that publications are found to be valid and findings credible. This is important to assist reviewers and the academic community to have confidence, whilst removing any flaws or erroneous studies from the literature.

Several approaches were discussed, through which a journal can assist the community in standardization, which included; (1) increasing transparency and reproducibility, by requiring publications to include a clear and detailed set of methods, (2) encouraging submission of benchmarking studies which include quantitative comparisons between devices, (3) publishing key figures of merit within the field and (4) acting as a forum for discussion to tackle controversial or troublesome issues.

The importance of standardization to be expert driven was raised and it was proposed that publishing can provide a vital platform to achieve this.

Nature Photonics have implemented a pre-submission questionnaire for manuscripts to ensure best practice is adhered to. This can include, for example questions, on statistical methods utilized or the origin of cells in the field of life sciences, and more precise questions for specific disciplines.

It was highlighted that it in certain cases, outlining standards in photonics can be challenging. For example, defining what constitutes as a laser is complex and remains widely debated within the community 60 years after its invention.

The efficiency of solar cells was a presented example within photonics that has benefited from standardization. Within this field, the challenge of mis-calibration was preventing quantitative comparison of efficiency between devices. By establishing stringent test methods characterized in official laboratories, this has resulted in improved efficiency over time. Only by adhering to these standards can solar cells now be considered, making any subsequent claims about the device performance 100% credible.

Nature Photonics are also interested in standardizing other areas of photonics such as super-resolution microscopy, to ensure the scientific literature is full of high-quality results.
Clinicians

EXPERIENCES FROM THE SAFEBOOSC CLINICAL TRIAL BY GORM GREISEN FROM RIGSHOSPITALET, DENMARK.

The key question from a clinical point of view is “are the devices ready in terms of accuracy and reproducibility to be used clinically?”, as it is vital a doctor only intervenes if they are certain it is beneficial to a patient.

Clinicians want devices to be as simple as possible, with clear thresholds to allow precise and reliable use, with clinical guidelines also important when establishing standards.

This phase-II randomized control trial involved a clinical consortium across 12 European cities, with the aim of examining the benefits and harms of cerebral oximeters in monitoring preterm infants. In this study an alarm was set based on the area under the curve indicating the burden of hypo- or hyperoxia in first 72 days of life. There were multiple potential interventions in both cases, including changing the pCO₂, fiO₂, vasopressure, airway pressure etc.

Outcomes demonstrated a statistical reduction in burden of hypoxia and hyperoxia on the brain when using cerebral oximetry compared to standard care.

Studies have also demonstrated that the repeatability on the same patient of recovered cerebral oxygenation (StO₂) values when devices were removed, reattached and reinitialized was poor, posing a challenge to standardization. Known issues are a dependency on the cerebral oximeters positioning on the head due to significant optical heterogeneity, and unknown degrees of arterial or venous contributions.

Results demonstrating a statistical heterogeneity in in vivo StO₂ values between different brands were also presented.

In order to fully assess the performance of these devices from a clinical perspective, a patient relevant outcome is also required, which is being carried out through the Safeboosc phase-III clinical trial.

European commission

AN OVERVIEW OF MEDICAL TECHNOLOGIES WITH EU SUPPORT BY BERND RAINER FROM THE HEALTH DIRECTORATE, DG RTD.

EU funding in MedTech has been steadily increasing between 1978 to 2013, arriving at over €1 billion in FP7 and the same amount only for the first half of Horizon 2020. Milestones include the 1st Medical and Health Research Programme (1978), a Biomedical subprogramme in FP3 (1990), a MedTech targeting approach focusing on SMEs through the Inno-2 call within the Health theme in FP7 (2011), and finally a fully bottom-up approach with the SME-instrument, completed by the Fast Track for Innovation, under the European Innovation Council pilot in Horizon 2020 (2014).

The funding and types of devices are both broad. For example, a number of success stories were presented, including genomic diagnostics beyond the sequence, fast-field cycling MRI, nanostructures containing contrast agents for both MRI and PET, 3D breast cancer models for X-ray imaging, 3D Printing for personalized medical devices, etc.
The H2020 - Societal Challenge 1 approach in calls for research proposals is a problem-solving and technology-neutral one, with both pre-normative and standardization aspects welcome to be included in the projects.

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**WORK ON THE EU METROLOGY PROGRAMME FOR INNOVATION AND RESEARCH (EMPIR) BY HEICO FRIMA FROM DG RTD.**

Metrology is the Science of measurement, such as traceability, calibration, references and standards.

EMPIR currently involves 91 projects in 8 thematic areas with €600 million funding.

Some funded examples were given, including MetVBadBugs to quantify drug penetration into Gram-negative bacteria, and PerfusImaging to develop physical standards and data analysis tools to assess the reliability of different imaging techniques for early diagnosis of cardiovascular disease.

Normative research is funded to help accelerate the development of European or international standards, for example EUCoM, which works on standards for the evaluation of uncertainty of coordinate measurements in industry. Future calls for normative research will be in 2019 and 2020. Further details are available at EURAMET www.euramet.org and EMPIR https://msu.euramet.org.

Diffuse optics is not currently represented in metrology, but representation in future is desirable.

USA has a high level of coordination between basic research and federal level, for example FDA have interest in care at patient level, an approach which is also desirable in Europe.

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**EXPERIENCE WITH TRANSLATION AND REGULATION IN NANOMEDICINE AND BIOMATERIALS’ IN THE H2020 LEIT NMBP PROGRAMME BY FERGAL DONNELLY FROM DG RTD.**

A deficiency exists in professionals who are both experts in their field, whether that be clinical, biological, photonics etc. and also have experience in regulations, which has an impact on KETs.

Medicines are regulated by the EU commission (DG SANTE) and EU medicines agency advises through specialist committees CHMP, CAT and PDCO. Pricing and reimbursement are still the prerogative of member states.

Medical devices are regulated by Member State Competent Authorities and the European Commission (DG GROW), and member states Independent notified bodies issue the CE mark.

Nanomedicines are a borderline between pharmaceuticals and medical devices, for example an asthma spray with a corticosteroid also requires a bottle sprayer. This poses a challenge for the developer regarding the appropriate regulatory pathway, although often both pathways are required.

A transition is occurring in medical technologies, with cross technology, cross industry and cross business model approaches. Project NOBEL combines KETs like nanotechnologies, photonics, robotics, advanced materials and information technology to build smart devices, which is developing a roadmap that incorporates SMEs.

Project REFINE brings together key stakeholders into regulatory science framework for the risk benefit assessment of medical products, examines the most pressing regulatory challenges and validates new analytical or experimental methods.
It is challenging to validate Biophotonics when the nanomedicines have not yet been standardized, with no current official definition of a nanomedicine.

FUTURE PROSPECTIVES

EU regulations

A SUMMARY ON NEW EU REGULATIONS ON MEDICAL DEVICES BY PAUL PISCOIO AND OLGA TKACHENKO FROM DG GROW.

Regulatory framework on medical devices in Europe is changing, expected to ensure (1) better protection of public health and patients, (2) more legal certainty and innovation friendly environment, (3) greater transparency and patient empowerment, and (4) a more European approach.

This includes 2 directives on regulation on medical devices (MD) (90/385/EEC & 93/42/EEC) and one the directive on in vitro diagnostic (IVD) medical devices (98/79/EC) are being replaced by the Regulation (EU) 2017/745 on medical devices and Regulation (EU) 2017/746 on in vitro diagnostic medical devices.

Entry into force of these regulations took place on 25 May 2017, planned to be progressively applied over the next 3 years for medical devices and 5 years for IVDs.

Better protection of public health and patients includes: stricter pre-market controls on high risk or substance-based devices, reinforced oversight from notified bodies, new provisions for clinical evaluation and investigation, inclusion of certain aesthetic implants, a new classification system on risks for IVD devices, stricter use of hazardous substances, and introduction of a unique device identifier tracking system.

More legal certainty and innovation friendly environment includes: EU regulations which are directly applicable in member states, clarification of scope for both MDs and IVDs, stronger role of the commission on regulatory status, clarification of specific applications and responsibilities of economic operator laid out, and medical software also now falls within the terms of MDs.

Greater transparency and patient empowerment includes: a comprehensive database on medical devices (EUDAMED) largely publicly available, implant card given to patients with implanted medical devices to make them traceable, summary of safety and clinical performance, legal obligations for manufacturers and authorized representatives on protecting damaged consumers / patients.

A more European approach includes: registration of devices at an EU level, improved coordination between member states in vigilance and market surveillance, strengthening of EU joint assessment procedure, and a coordinated assessment of clinical investigations in many member states.

Patients and clinicians EU organisations are directly and actively involved in drafting of guidance, with stakeholders from the patient interaction, including the European Patient forum, and clinical stakeholders amongst which the Biomed alliance. A call will be made for participation from the scientific community as organisations. A second call for scientists to participate as individuals in scientific panels will follow next year.

An issue was raised that innovation friendliness is important, as getting permission from a device agency is the same paperwork in early stage preliminary investigations as it is for advanced clinical investigations, and these can vary in different member states. To assist with this, multi-center, multi-stage investigations can be approved at once.
A concern was raised that stricter rules are making it harder for small companies with innovations to get to the market, however the mechanisms are designed to be tougher on those in charge to ensure proposals are very strictly followed for improving patient safety.

**CHALLENGES AND OPPORTUNITIES IN STANDARDIZATION**

**Challenges**

- Establishing the level of standardization required, whilst avoiding hindering innovative and disruptive research.

- Devising test-ship-test protocols to overcome the logistic challenges when transferring phantoms between laboratories and ensure phantom validity is maintained.

- Although consortiums such as the photoacoustic initiative highlighted in Cambridge are an excellent way of bringing people together, acquiring funding for these types of consortiums can be difficult.

- Assessing the performance of devices when used in practice within the clinic can be more difficult, such as the impact of motion or response to ambient temperature changes.

- Many commercial cerebral oximeter systems are “black box” in nature, with manufacturers not wanting to disclose algorithms, data processing or the origin of look up tables, contributing to device variability.

- Determining from a clinic perspective the level of quality control and quality assurance required, and what constitutes appropriate performance.

- Deciding who will define the standards, whether they will be mandatory, and how to ensure widespread adoption is achieved.

**Opportunities**

- National and international collaboration between groups can enable best practices to be shared and facilitate comparison studies between systems using the same standard phantom.

- 3D printing can provide a low cost, easily reproducible approach for constructing phantoms.

- Wider, open accessibility to benchmark datasets can accommodate the algorithmic progress being made in artificial intelligence and machine learning.

- Integration of several other disruptive medical technologies within the standards for Biophotonic devices, such as new biomarkers (both genetic and physiological), stem cells to regenerate tissue, 3D printing of biomaterials for artificial organs, improved sensors to monitor body functions, IT networks to enable remote care, big data / machine learning / AI for better diagnosis and augmented reality / assisted healthcare in surgery.
OUTCOMES FROM WORLD CAFÉ DISCUSSIONS

Workshop attendees were divided into seven working groups focused on either: diffuse optics, fluorescence, mammography, OCT & ophthalmology, oximetry, photoacoustic or Raman, with the following questions posed to simulate discussions:

1. How do you evaluate the performance of a device (e.g. phantoms, test bench of basic parameters like voltage or current, in vivo tests,...) and when (e.g. at factory level, on site after installation, scheduled calibrations, ..)?

2. Do you use phantoms? Is it a simple homogeneous phantom reproducing a limited set of parameters (e.g. homogeneous phantom, reflectance standard) or a more complicated structure (e.g. lay8ered or dynamic phantom)?

3. Are you in favor of adopting guidelines and / or standards to evaluate the performance of a device?

4. Who should be in charge of evaluating the performances of a device: manufacturer, end user, national / European authority, researcher, other?

5. What action should be started to promote standardization activity? Network, ..., other, none?

6. Is there an acceptable risk for the patient if the accuracy or other performance specifications are not met (“essential performance”)?

7. What is the relative value of performance characterization by phantoms vs. clinical validation for the technologies discussed?

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Diffuse optics

Discussions focused on the use of phantoms, specifically whether a single phantom is appropriate for all fields of Biophotonics, or whether each field requires more specific phantoms.

There exists some requirements of phantoms and general aspects of standardization in DOI which are common between fields within Biophotonics, such as the importance of absorption and scattering properties, so it may be possible to have a single phantom for these shared standards.

However, it was also agreed that certain fields will require more specific standards in phantoms, for example the speed of sound in photoacoustic imaging, so a subset of phantoms may be required to address these more specific questions.

This variety makes it important for representatives from all fields to come together and share best practices to learn from each other.

The consensus between the experts was that static and dynamic phantoms are both useful, with static phantoms playing a role in technical characterization of the instrument, whilst dynamic phantoms provide more clinically relevant information as they are often more representative of the biological processes of interest.

Another important role of phantoms is to establish a quantitative benchmark for clinicians of the instruments expected performance in vivo, for example the blood phantoms used by Martin Wolf, such that devices can be reliably used in a clinical setting.
A clinician within the group commented that “Usually, we (clinicians) are not satisfied with the absolute values that most systems give”, a point which it will be important to address by standardization.

The question of how to implement a common standard phantom in practice was discussed, with an approach suggested that an individual phantom, or set of approved phantoms, could be established which could then be shared between labs, allowing direct comparison between systems.

The potential to learn from other well-established medical imaging modalities, such as MRI or CT, was also highlighted, to observe how the standards currently used in these fields were established over time. For example, it will be important to learn from modalities which have similar issues in terms of standardization, such as how they produce and use phantoms in the context fMRI for fNIRS development and the standardization of protocols in electrical impedance tomography.

Fluorescence

For standardization in FMI, there is a need to characterize many parameters, including sensitivity, resolution, depth sensitivity and dynamic range.

This can be achieved using tissue phantoms such as the state-of-the-art work already outlined by Dimitris Gorpas. These phantoms need to be multispectral, with a range of wavelengths implemented in FMI.

Some desired outcomes for devices from standardization of FMI were proposed as; (1) it needs to function in a clinical setting, (2) it needs to be robust over time and (3) it needs to be insensitive to movement artefacts.

It was suggested that standards in FMI may need to vary depending on the application, for example the spatial resolution required in surgery can be different for endoscopy or diascopy.

The question was raised of whether it is best to have several different phantoms or one master sample for everything. 3D printing may facilitate a potential approach for building identical phantoms in a reproducible way.

A unique challenge to FMI is photobleaching of fluorophores, which occurs as soon as tissue is exposed. This can be overcome to some degree through use of quantum dots with long lifetimes.

Applicable to all Biophotonic devices, in addition to standard phantoms, it is important to explore whether protocols also need to be standardized to achieve these outcomes, to take account of any human dependency on performance.

Clinicians must be involved, and their needs must also be considered when establishing standards. For example, it may be desirable to have an automated and fast interoperative standardization protocol, but first it will need to be assessed whether it is possible to measure using a phantom during surgery without negatively impacting the surgeon.

It was highlighted that biological tissue itself isn't standardized, with optical properties variability having a quantitative impact on the fluorescent signal, so further information about these properties are needed for quantitative interpretation of the signal. It was suggested that to attempt to account for this, standardization could also incorporate appropriate models of light propagation, which could be Monte Carlo or diffuse optics based.
A framework of standardization was suggested, where the level of standards will vary at different stages of the project, with less at a research level than a clinical level, ensuring that regulatory work is not hindering development.

Finally, once standards have been established, it will be important for rigorous comparison studies to be carried out to validate the standards.

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**Mammography**

In mammography, either diffuse optics or fluorescence signals are used to diagnose cancerous tumors in breast tissue.

The typical stages of standardization in mammography were outlined as, (1) characterization of performance of individual components, (2) testing overall system performance in the laboratory using phantoms, (3) repeat phantom tests in a clinical environment to ensure performance is maintained in suboptimal conditions & (4) finally tests *in vivo* comparing healthy and diseased subjects.

For standardization, the durability of phantoms is important, making solid, polyurethane-based phantoms preferable in this regard compared to liquid or fluorescence phantoms which are harder to work with.

Opinion from the experts was that standards and guidelines are certainly needed but should not introduce excessive constraints or be unnecessarily complicated, and there will be a trade-off between what is required for assessment of performance and what can actually be done in practice.

It was proposed that although manufacturers should ultimately be in charge of evaluating device performance, the end user should also have the knowledge of how to test performance.

A web platform was proposed through which expertise could be shared including recipes for phantoms, the existence of phantom kits to be circulated and example datasets. To develop such a platform will require funding and importantly someone to be responsible for managing this over a long time period.

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**OCT & Ophthalmology**

The range of protocols used by the experts in evaluating the performance of systems in OCT can include analysis of single parameters, the use of non-standardized homemade phantoms or testing on biological samples.

Phantoms in OCT vary from homogeneous monolayered types to heterogeneous, complex phantoms, which can, for example, simulate vein structures.

Standardization is commonly incorporated into the operating software, in which warning signals during acquisition inform the clinician when a device is not functioning properly.

One issue raised was that during phantom development or when testing with biological samples, it is desirable to simulate as closely as possible what is typically observed in a clinical setting, however in some cases it can be hard to define what normal properties of subjects are, either within healthy or diseased groups. An example of Alzheimer’s within OCT was given.
Biological samples assessed using OCT are all very different in optical properties, for example between applications in ophthalmology, bronchoscopy or skin cancer, so the experts believed it was necessary to have multiple phantoms that each consider a specific application.

Phantoms are needed not only to assess the technical performance of a device, but also to assess the data processing steps, particularly when comparing different instruments.

A national regulatory body should be established utilizing standards set by the EU which approves application to patients and commercialization.

This working group gave the opinion that all risks are unacceptable, and safety should be paramount in standards, for example, controlling the laser power. In all cases, even for applications without essential performance, many false positives or negatives can lead to risks in the economic aspect and to the wellness of the user.

Phantoms bring a consistency and can ensure inter-operator repeatability, whilst it can be challenging to carry out repeat studies using a clinical sample.

Simple phantoms which don't recapitulate the actual biology can be enough.

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**Cerebral Oximetry**

This working group expressed that for standardization to be effective, interest from researchers needs to be matched by funding bodies and it must be considered as high-level research.

This will require publication on reproducibility and performance of systems in high rank journals, to encourage more people to work on standardization and quality assessment.

Phantom procedures can be more challenging to implement in a clinical environment, for example, the use of real human blood can pose health and safety issues making the development of a phantom that accurately mimics blood desirable, so that real blood does not have to be used.

Some concerns were expressed over the level of additional paperwork and costings for basic, preliminary research. A potential route for research level medical devices to fast-track to preliminary studies in clinics would be highly desirable, particularly with highly safe optical devices with negligible associated risk.

Further feedback from the community could also be obtained via an online questionnaire survey.

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**Photoacoustic**

PA imaging demonstrates large potential but is also a method in its infancy in comparison to other Biophotonic techniques.

As devices are typically very application specific, it was suggested that standards may need to be unique on a “per organ per application” basis.

Phantoms are important to test the capability of a PA device in laboratories and then function as a quality control process during clinical application.
Phantoms are typically more complex than in other fields, as they need to account for both optical and acoustic properties, and again depend on the application. For example, the test required for performance are very different depending on whether you are interested in imaging the skin surface or the interior of the breast.

A desire was again expressed for an effective blood mimicking material.

Experts expressed that a bottom up, grass roots initiatives approach, such as that presented by Joseph et al. in the Cambridge initiative, was the best model for integrating standardization and growing PA into a mature field, where the requirements from phantoms grows from the community.

Standardization will require mobility funding to exchange materials or travel between labs. It was felt that the role of industry will be important in this regard and should be promoted.

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Raman

The Raman signal is specific to the molecular composition of a sample, meaning no phantom is appropriate as its properties would always be slightly different from sample itself. Phantoms are therefore not used in Raman.

There is a requirement for standards on the calibration of intensity and wavenumber, which should be carried out on a daily basis with a device.

Many aspects of RS are hard to standardize, as performance depends on for example the material, sample size, substrate and the type of sample (fixed biological or live). The experimental protocol must also be adjusted according to the scientific question and nature of the sample, although the experts felt it could be partially standardized for a specific application.

Some areas which the working group believe could be standardized included the acquisition parameters, model evaluation and cross validation.

Manufacturers currently can evaluate automatic calibration of spectra, but other elements of performance need to be assessed by the end user or specific researcher, whilst in clinical applications both the end user and national authorities will need to be involved.

Some actions are already underway for standardization of RS in clinics through inter-collaborative projects, comparing differences in RS measurements from the same or different equipment, which need to be further promoted by regulatory bodies with allocated funds.

The acceptable level of risk depends on the application. For in vivo studies, safety standards are important, particularly of laser power as Raman is a very weak signal, whilst for ex vivo studies the diagnostic accuracy is important, although RS is not currently used in isolation for diagnosis.
CONCLUSIONS

Significant progress in knowledge of instrumentation and software within the Biophotonic means now is the appropriate time to address standardization. This workshop has acted to initiate this process, discussing some of the opportunities for improving performance through standardization, but also raising questions on the potential barriers in each of the respective subfields that will need to be addressed by the community. Feedback from experts in research, clinics, industry, regulatory authorities and the EU commission has highlighted the current need for standardization to fulfill the potential demonstrated in Biophotonics. Biophotonics already has over 15 years of EU collaborations, and future cooperation between these key players through strong links with the EU will be important for establishing an international consensus. Widespread adoption of these standards will be crucial in driving new technologies to the market and enabling clinicians to trust diagnostic information from devices.

One key issue addressed during the workshop was the need for careful consideration of the specific devices and applications in each field of Biophotonics when deciding on the appropriate type of phantom and its level of complexity for evaluating performance. Benefits were demonstrated in the context of comparing different devices through the use of dynamic, blood phantoms in cerebral oximetry, multiparametric, composite phantoms for high fidelity fluorescence molecular imaging and complex multilayered phantoms in optics-based, multimodal breast imaging.

Another key theme throughout this workshop was the need for multicenter studies, which encourage comparative studies between different devices, the sharing of protocols and data processing methods, and the provision of open source, benchmark datasets, all of which will require support from both the funding bodies and scientific publishing representatives, to ensure best practices are being implemented and to make outcomes reliable and repeatable.

When establishing a common EU strategy and an international consensus in these standards, it will be important to ascertain from the community the correct balance of regulation and standardization, such that performance and patient outcomes are improved, whilst at the same time not hindering disruptive innovation. Finally, strong communication between developers and end users will be crucial in further cross-sectional meetings such as this, to ensure a patient orientated approach is taken.