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Stakeholders and Communication Division

Meeting report - ICH E6(R3) Good Clinical Practice workshop with PCWP and HCPWP

3 June 2020, 09:30hrs to 13:30hrs – virtual meeting

Co-Chairs: Juan Garcia Burgos (EMA), Fergus Sweeney (EMA)

ICH E6(R3) Good Clinical Practice workshop with PCWP and HCPWP

Welcome

Juan Garcia Burgos (EMA) and Fergus Sweeney (EMA) welcomed participants and introduced the objectives of the workshop. As part of the Good Clinical Practice (GCP) renovation process, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has agreed to reach out, in particular, to academia and patients and the workshop is an early step of that process.

The workshop follows previous discussion held at the PCWP/HCPWP meeting on 3 March 2020.

1. Setting the scene

In her opening remarks, Kaisa Immonen (PCWP) commented that there is a need to renew the international GCP guidelines because the changes in the environment in which clinical research is taking place and the way clinical trials are conducted are changing rapidly. There are opportunities such as the use of big data, integrating real world evidence and using digital tools which are becoming mainstream and new technologies may impact the way clinical trials are designed and conducted. Once adapting to these new realities, some aspects of GCP may need to be made more proportionate but it will also be critical to ensure that fundamental ethical principles continue to apply to all research and that the guidance helps researchers in a practical way to run trials that are of high quality and yield robust and relevant patient data. Ultimately the aim is to create new treatments that bring concrete benefits to both patients and the society. One thing that has undoubtedly changed in the last years is the role of patients; their active involvement in research is no longer questioned, from setting priorities to designing and implementing clinical trials, and their added value has been confirmed. The questions now revolve around how best to realise the potential of patient involvement. It is critical to provide more extensive input in the next steps of this international process.

Ulrich Jaeger (HCPWP) reinforced that, as Kaisa mentioned, it is all about patients. However, healthcare professionals need guidance and tools to work in a proper way. The workshop is much welcomed as well as the interaction that took place so far. As the different patient and academic

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speakers will illustrate, sometimes guidelines may risk being more inhibitory than helping patients and one of the ideas of the renovation is to get clear guidance of what is helpful and what is not in conducting clinical trials. The expectation and aspiration are to have a final guideline which will be helpful for everybody.

Fergus Sweeney (EMA) complemented the opening remarks by mentioning that ICH is in its 30th year and that certainly the agreements made in the 90's to enable a single clinical development for a medicine on harmonised standards around the world have been enormously beneficial in streamlining the development of medicines and ensuring that they can reach patients in an effective way and with good clinical data as a basis and that can avoid redundant clinical trials in different parts of the world run to different standards. It is however time now to have a look again, to rethink, to consider opportunities in development and the way clinical trials are conducted.

1.1 Introduction to the ICH guideline development process

Lenita Lindstrom (EC), Milton Bonelli (EMA) and Edit Szepessy (EC) provided an introduction to ICH - The 'International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use' – as an organisation, to the ICH guideline development process and to the Clinical Trial Expert Group (CTEG) involvement in the review of the E6 concept paper (see presentation).

ICH started in 1990 at the initiative of the European Commission in an informal context reaching out to the Japanese regulators (MHLW/PMDA) and the US FDA together with their regions' own research-based industry organisations and with Health Canada and Swissmedic as observers as well as IFPMA and WHO. In 2015 following several years of discussion ICH was substantially reformed with a new governance model aimed at ensuring global outreach to other regulators and increase transparency, with regulators in the driving seat although recognising that industry provides key scientific input to its processes. This led to the setting up of ICH as an independent legal entity, non-profit association under Swiss law, with a permanent secretariat based in Geneva.

ICH's objectives are to improve efficiency of new drug development and registration process as well as to promote public health, prevent duplication of clinical trials in humans and minimise the use of animal testing without compromising safety and effectiveness. These objectives are accomplished through the development and implementation of harmonised Guidelines and standards. ICH is not harmonising legislation but rather technical and scientific requirements in the fields of safety, quality and efficacy. ICH Guidelines are not legally binding but one of the key success factors has been that the regulators have been implementing those agreed guidelines in a consistent and harmonized manner.

Within the ICH governance, the Assembly is the main decision body. Guidelines are developed at the level of expert groups and then adopted by the regulatory members of the ICH Assembly.

There are not yet any patients or healthcare professional organisations involved in ICH. In order to qualify to become an observer in ICH such an organisation would need to be an international one, with global coverage. Eligibility criteria can be found in the ICH website. **ICH would very much welcome to have in the future an international patient organisation and an international healthcare professional organisation with an interest in ICH, applying and officially becoming an observer in ICH**. In the meantime, ICH reaches out to these stakeholders by publishing information in the ICH website (www.ich.org) and in the area of E6 – which is one of the most important ICH guidelines – by holding this type of workshops which are done in different ICH regions.

The EC works very closely with EMA in ICH. EMA is coordinating the input from experts through the EU regulatory network by reaching out to its scientific committees and working parties.

ICH has a yearly structured cycle for selection of new topics or work products (such as a revised

guideline). These can be proposed by any ICH member or observer party. Topics are triaged by a subgroup of the ICH Management Committee and Assembly members and then a final decision is made at the June face-to-face ICH meeting (for example the 3rd revision of the E6 guideline was selected at the ICH June meeting in 2019, in Amsterdam). There can be an individual guideline project or, as it is the case for the E6 guideline, there can be a broader project such as the ICH GCP renovation project where various guideline drafting processes are covered.

The ICH guideline development process follows 5 main steps, starting with the consensus building for a technical document (step 1) all the way to adoption of the harmonised guideline (step 4) and subsequent implementation by ICH regulatory members in their respective regions (step 5). The core aspects of the drafting work are run by a core group – the ICH expert working group (ICH EWG) – formed by regulatory and industry experts; for E6, as for all ICH WGs, the composition of the EWG can be found in the ICH website. Further input is then given by a broader plenary working party, which is consulted at regular intervals.

Regional public consultations (step 3) are organised following a formal adoption of the draft guideline by the ICH Assembly (step 2b). At EU level, the draft guideline for consultation is adopted by CHMP. The same procedure applies for the adoption of the (final) guideline at step 4. ICH guidelines supersede EU guidance documents while providing a useful framework for pharmaceutical and clinical research. ICH GCP is embedded into EU legislation (which is rare).

The Clinical Trials Expert Group (CTEG) is a group chaired by DG SANTE and consists of one expert from national competent authorities responsible for clinical trials and one expert from ethic committees from each member state. EMA is an observer in this group. The CTEG became involved in the ICH GCP process in November 2019. This collaboration provides an EU-wide forum of ethics and competent authorities' experts for review and opinion and, together with the Clinical Trial Facilitation Group of the HMA (CTFG), support a strong and harmonised European position in the ICH discussions.

1.2 Introduction to ICH E6(R3) and stakeholders' engagement

Lisbeth Bregnhøj (DKMA) gave an overview of the ICH E6 guideline revision addressing its history and purpose, the stakeholder engagement approach, and the progress so far and expected next steps (see presentation).

ICH E6 was originally finalised in 1996 and describes the responsibilities and expectations of all stakeholders in the conduct of clinical trials, with the two responsible parties being the sponsor and the investigator. It covers aspects of monitoring, reporting, and archiving of clinical trials and included separate addenda with the essential documentation needed to support the clinical trial and the investigator brochures. There have been two revisions throughout time with the last one finalised in 2016. This was not a complete opening of the guideline but rather an addendum to encourage the implementation of improved, risk proportionate and more efficient risk approaches and updated standards for electronic records. Already at that time **it was recognised that the guideline was due for a larger revision to incorporate among others academic stakeholders concerns** which called for improved focus on issues most critical for trial quality, and pointed to the need for some flexibility to conduct different types of trials rather than the one size fits all approach of the guideline and highlighted the importance of involving academic stakeholders in the ICH processes. This ultimately led to the 2017 reflection paper describing the renovation of the efficacy(E) guidelines ICH E8 (on the general consideration for clinical trials; focusing on the clinical trial design principles) and ICH E6 (on good clinical practice, focusing on the clinical trial conduct principles).

The draft version of ICH E8(R1) released for public consultation in May 2019 already includes references to engaging with stakeholders in study design (3.3.3), including patients and treating physicians, and to the need to build on accumulated experience and knowledge with periodic review of

critical to quality factors (3.3.4).

The purpose of the E6(R3) revision is to acknowledge the diversity of trial designs, data sources, and the different contexts in which clinical trials can be conducted as well as to highlight that GCP principles can be satisfied in a variety of ways. Contrary to what happened with E6(R2), this revision is calling for a complete rewrite and reorganisation of the current guideline. The aim is to provide a principles document describing the overall principles applicable to all clinical trials (e.g. that patient safety prevails over scientific and society interest; that an informed consent is needed; that data should be reliable) and complement it with two key annexes – one covering interventional trials, reflecting the concepts already included in E6(R2) with updates and refinements as needed; and another addressing considerations for non-traditional interventional clinical trials, such as pragmatic clinical trials, decentralised clinical trials and trials that incorporate real world data sources. The revision is also looking into alignment with E8 as appropriate and bridging identified gaps of E6, some of which already highlighted by various stakeholders, but also gaps between E6 and other ICH guidelines. In addition, the revision is aiming towards a clear and concise scope to avoid its overinterpretation and to focus on key concepts such as quality by design, risk-based approach, proportionality and critical to quality factors.

ICH E6(R3) EWG is following the approach of simultaneously working on the principles and Annex 1 first, as identified in the E6(R3) concept paper endorsed in November 2019, and once Annex 1 has been developed (and has started in the public consultation phase) then prepare annex 2 having further defining of the scope will take place. The process leading to the overarching principles document and Annex 1 is expected to take approximately 24 months to reach step 1, which means the public consultation phase could be expected to start towards end of 2021. In the meantime, and as outlined in the summary of the E6(R3) stakeholder engagement approach, ICH wants to engage with stakeholders in the early development phase.

ICH is piloting a new way of engaging with stakeholders for the E6 renovation as there are many different stakeholders impacted by the guideline, including patients, consumers and healthcare professionals. ICH has therefore committed to stakeholder engagement initiatives in order to understand their perspectives at an early stage of the guideline development process, as the EWG develops the principles and annexes (step 1), and not only when the public consultation stage is reached (step 3). Two types of engagement are foreseen. The first includes a regional public engagement approach via existing mechanisms such as meetings like this workshop and surveys, where each region will decide how this is to be organised. The second type of engagement involves participation of the stakeholder representatives in direct interactions with the ICH EWG. The intention is to have representatives selected from academic clinical researchers and other stakeholders - and for Europe that will be done via PCWP and HCPWP – to engage in both face-to-face meetings of the EWG (twice annual meetings) as well in teleconferences as needed. The goal is to seek input on relevant issues such as experiences with clinical trials and insights on the most challenging aspects of applying GCP. The EMA will make a request first to the HCPWP and then PCWP for the appointment of these representatives.

Through this engagement it is anticipated to **develop a guideline which is responsive to the needs of those conducting or participating in clinical trials**. This external outreach will provide transparency as well as improved understanding and implementation of the guideline with an expected smoother adoption by stakeholders.

Following the endorsement of a business plan and concept paper in November 2019, the EWG was officially established and has since been working on drafting the principles as well as the scope and content of the guidance. In June 2020 the stakeholder engagement activities were initiated in different regions with this workshop with PCWP and HCPWP being the one for Europe (with one for the Americas

for example on the days following this meeting). The EWG will then discuss on their regular teleconference what were the lessons learnt from these engagement activities and how to include them in the work of the guideline.

1.3 Clinical Trials Transformation Initiative (CTTI) survey results

Pamela Tenaerts (CTTI) presented the results of an independent initiative aimed at providing an opportunity to multi-stakeholders to give feedback to the ICH update of E6 (see presentation). CTTI - a multistakeholder, public-private partnership co-founded by Duke University and FDA – conducted an online survey in Summer 2019, to identify the areas of ICH E6 that were or were not in need of updating and selected a diverse group of stakeholders for in-depth interviews. The qualitative, in-depth telephone interviews took place in Autumn to explore what stakeholders hoped the update would achieve, what were the most and least helpful aspects/sections of the guideline and why, and how the guidance could be improved. An open-comments platform was also created after the survey was concluded to seek comments on how the text of the guideline could be improved.

Pamela underlined the **large role played by European respondents in the survey, with 60% of participants located in that region**.

The findings of the three components of the CTTI initiative are detailed in separate reports together with an explanatory webinar which can be found in their website. In summary, the **evidence gathered determined that the areas requiring the most focus were those related with sponsors (monitoring), essential documents, and investigators**. The need for flexibility, simplification and updating to accommodate changes in research conduct and technology as well as to clarify terms and concepts were also highlighted. The results also showed a strong call for transparency and inclusiveness, with clear requests for inclusion of a wide variety of stakeholders in the review process and transparency around the creation of the renovation (process followed, rationale behind decisions, stakeholders who are involved and how they are selected, process for soliciting feedback and how feedback was reviewed).

2. ICH E6(R3) GCP Expert Working Group perspectives

2.1 ICH E6(R3) GCP EWG

Rebecca Stanbrook (EFPIA) provided further insight into the ICH E6(R3) GCP Expert Working Group (EWG) work and an overview of the thinking behind the current E6 renovation with a presentation jointly prepared with other experts involved in this working group, namely Gabriele Schwarz (BfArM), Lisbeth Bregnhøj (DKMA) and Susanne Nørskov (EFPIA), who bring together extensive experience in GCP inspections and in the pharmaceutical industry (see presentation).

Rebecca reiterated the **need to update the E6 guidance as the world has changed greatly since 1996 and even since the latest renovation (R2) in 2016, with the evolution towards a new digital world and different trial designs**. As the E6 EWG is starting to think about the principles, gathering input at this early stage is of vital importance. When considering the necessary updates, the EWG is looking into the E6 guidance and the interdependencies with other guidelines as well as identifying potential areas for intensive update such as clinical trial design, sponsor and investigator roles and responsibilities, safety information and investigational medicinal product, keeping in mind that trials are not only for registration purposes but can provide standards for the future care of patients.

The essence of good clinical practice encompasses the protection of participants, the generation of reliable results and proportionate procedures and documentation. Whilst ICH E8 general considerations of clinical studies set out the overarching principles for clinical trial design and protocols, there are several elements that feed into the conduct of clinical trials that are covered in

other ICH guidelines. Some of these have also either been recently updated such as ICH 9 on statistical principles for clinical trials (adopted in November 2019) or are undergoing revision such as ICH E19 on the optimisation of safety data collection (currently under public consultation). All these need to be considered when looking into the ICH E6 renovation.

In relation to clinical trial design, for some years there has been an increasing number of patients engaged in the design of trials, but this is still not enough. When looking at the informed consent, particularly in pharma trials, they continue to get longer and less understandable for the lay person. The studies' endpoints might not be the most important ones for the patients – a good night sleep might be significant in their quality of life but might not be considered by the sponsor. We see more and more that participants have data collection tools such as mobile phones and wearables that are part of their daily lives and these could also be useful within clinical trials. Participants are often burden with a large battery of tests which might not be overall useful for the endpoint of the trial and mean increased visits. There is therefore a need to make trials more patient-centric, including for examples that some of the visits happen in the patient's home (as seen during the COVID-19 pandemic).

It is recognised that increased **participant involvement in trial design** will support more readily understandable informed consent documents, trials objectives that are more relevant for the participants, and the identification of data collection tools that are already part of their everyday lives ultimately lowering the burden not only for participants but also for the healthcare professionals.

For healthcare professional, it has also been seen that clinical trials are not always fully considering the standard of care for the disease or may exclude a larger number of potential participants due to extensive inclusion/exclusion criteria. As for participants, there can be a great burden due to the use of different data collection tools from different sponsors – it is common to see in an investigator site with many different sponsors with different data collection tools and that causes additional burden. The collection of additional data points which might not be important also increases the burden for the **healthcare professional**. Therefore, their **involvement in trial design** is also very important.

Clinical trial designs have changed over the years and non-traditional designs will be included in annex 2 of ICH E6(R3). These trials would still be able to be conducted within the realms of annex 1 of the guidance but annex 2 will provide some additional considerations (information and guidance) for the different non-traditional designs and data collection methods (platform trials, pragmatic trials, umbrella trials, decentralised trials, digital developments and real world evidence). We have seen the use of platform and decentralised trials during the COVID-19 crisis and these different trials are being increasingly recognised as in need to be included in E6(R3). The development of more digital tools in a fast-changing world also need consideration. We see an increased use of real world evidence in submissions and in the design of trials and this is clearly another area where guidance would be useful.

Another aspect which needs to be considered is **sponsor oversight and responsibilities**. All trials are not created equal and a risk-based concept should be considered throughout the trial. This was brought in in E6(R2) however further detail would be appreciated. In terms of service providers there is an increased blurring of lines in the investigator sites with increased use of subcontractors/services providers being suggested by sponsors and thus clear agreements need to be in place to ensure qualification and oversight with an appropriate level of understanding of who is doing what (e.g. a home nurse might have been contracted by the sponsor but ultimately the responsibility and oversight of their activity needs to be with the investigator). We also see an increased use of data safety monitoring boards (DSMBs) and adjudication committees and further guidance at this level might be useful. With regards to monitoring obligations, these need a risk-based approach, however, still ensuring the safety of the participants and accuracy and integrity of the data. From a sponsor perspective, the informed consent process needs to be appropriate and providing the right information so that participants are able to understand the trial and the protection of their rights. We have seen

some sponsors' consent forms which want the patient to wave their rights, for example accessing their data remotely without adequate data security and data privacy protection. It is recognised though that in the advent of telemedicine this may have an impact on how informed consent is taken. Throughout the guideline there needs to be a proportionate approach, with focus on what are the important data points for consideration.

From an **IT perspective** we see a digital age where there are ever more data collection tools. Although E6(R2) brought some guidance it is now clear that more is needed in this area. Consideration needs to be given to tools being fit for purpose, capturing the protocol information and designed in such a way they meet acceptable feasibility and performance characteristics such as accuracy, precision, and consistency of measurements over time, and uniformity of measurements across technologies. IT systems also need to consider data privacy aspects although it is recognised there are different regulations globally. The security of systems and software is of paramount importance not only from a participant right's perspective but also from an organisational perspective. The landscape in which trials are taking place is becoming very complicated with multiple parties involved in the data entry process and using different IT systems, not only for large organisations but also with investigator-initiated trials. This requires robust computer system validation (CSV) to ensure data integrity and data transfer protocols, so no data is lost or changed when moved between systems. From a data protection perspective, consideration for where the data resides, who is the owner and who is the data controller is also needed. Separate to the legal concept of "data controller" it is also very important that the investigator retains control of the data they generate and report in the sense of what is recorded and what changes or corrections can be made to it. ICH E6(R3) will not write a set of CSV guidelines but it will be helpful to include some principles addressing data integrity and trial result reliability from an IT perspective.

From an **investigator perspective**, proportionality is essential. As already mentioned, the identification of what are the important data points to ensure participants' safety while answering the research question; using risk-based approaches and clarifying how the investigator ensures the adequate supervision of delegated activities to home nursing, general practitioners or satellite centres/sites and local laboratories are critical. The incorporation of telemedicine in routine care will benefit investigators as well as participants and consideration needs to be given to how this could be used in the clinical trial setting. There is also an increased emphasis in the use of electronic patient reported outcomes and some trials are encouraging the 'bring your own device'.

Up to date **safety information** needs to be available to the investigator and participants in a timely manner. We are aware of cases where investigators have been provided with huge volumes of information which has not been well thought through by the sponsor but sent just to tick a box (or indeed hundreds of boxes). We are also seeing use of available data from other sources (compassionate use, real world) to guide the collection of additional information. Again, proportionality is key in safety reporting. This is being planned in E19 to avoid duplication of effort, looking into what safety data is important and the format and frequency of dissemination of that information to investigators. E8 revision is also covering considerations on the design of a clinical study which should reflect the state of knowledge and experience with the medicine. These elements of proportionality will also be included in E6(R3).

Investigational medicines have changed over time with more personalised medicines involved and with different mechanisms of shipping these medicines to patients. For example, decentralised trials during the COVID-19 pandemic are using direct to patient shipments as an exception to national regulations or practice. Regulators are collecting experience on this practice and it has been recognised that this could be potentially valuable to some participants in certain circumstances. In these cases, points to consider include the level of accountability that needs to be undertaken (e.g. a large cardiovascular outcome trial might not need the same degree of accuracy in drug accountability

records as perhaps an oncology clinical trial), data privacy aspects and storage condition requirements. Additionally, how to maintain investigator oversight (e.g. when due to the complexity of the treatment regimens and different routes of administration, a home nurse needs to go to the patient's home to administer the medicine which has been directly delivered there). Also, what information is provided to the participant about the drug the shipment, handling, storage requirements and directions for use? When the sponsor is responsible for this shipment, how to preserve anonymity of the patient files? Consideration of the patient population is essential - for example, is it acceptable to ship directly to vulnerable or elderly persons? In summary, the ICH E6 R3 Expert Working Group wants to draft a GCP guideline which is modernised and fit for purpose and for that the engagement of academia and patient advocacy groups is vital.

3. Patients, consumers, healthcare professionals and clinical researchers Perspectives

3.1 PCWP perspectives

François Houyez (EURORDIS) illustrated in his presentation aspects important to patients and highlighted that the ICH E6 revision was an excellent opportunity to revise or even set new standards for clinical trials (see presentation).

In terms of the scope of the E6 guideline, the revision could, for example, consider going beyond "pivotal" trials, also called regulatory trials. There are **treatment strategy trials** with authorised medicines that could be used to answer questions such as: which products work best when first line treatment fails? How to combine different medicines to increase the treatment effect? Also, we have seen that sometimes observational studies with an **off-label use** are not always registered as clinical trials. Maybe there is a need to clarify when is a medicine considered as part of an interventional study and when it is not, as part of considerations to be included in annex 1.

ICH standards are mostly for the development of medicines but sometimes **medicines** are **combined with medical devices** and we need excellent and high-quality research in medical devices too. From a patient and carer perspectives is hard to understand why we need different standards for trials to test medical devices. More flexibility is needed to have a global standard for all types of medical interventions.

Comparing an investigational medicine to standard of care in 2020 cannot use the same reasoning as that used back in the 90's. At that time there were much less medicines and standard of care consisted of few options. The **concept of standard of care** is more complex to discuss in our days. We will probably have an increased number of clinical trials that combine investigational medicines with other types of treatments.

The conduct of clinical trials is evolving and we can foresee today **trials that are almost completely virtual** with the use of telemedicine to ensure contact with clinical investigator/research nurse, with connected devices to measure patient outcomes, with the investigational medicine being shipped to participant's address, and with e-consent and dynamic consent that could be made online. Almost all aspects of clinical trials could be made virtual or have a mixed component, combining visits to the clinical trial site with virtual participation.

The **size of patient populations** also needs consideration. In the 90's, trials needed large populations of 3,000 or more trial participants to be exposed to the investigational medicine before a dossier could be submitted. In an era of precision medicine and rare diseases there is a need for new approaches to generate the quantity and quality of data needed. Particularly in the field of rare diseases, there are difficulties in current enrolment for clinical trials. And there are now current technologies that can be used to generate more data with less patients. For example, using a simulation case study in Parkinson's disease, François showed how most of the events that affect a patient's daily life are not captured in the clinical site visits and if these could be captured for a single patient you would increase

the available data to measure an effect of the treatment and have a much larger data set with the same small number of patients.

There are other examples, such as adaptive trials with a single arm with large effect size, where we need to adapt to address changes in the way clinical trials are conducted. We should explore **multifactorial trial design**, testing different investigational medicines within the same clinical trial and maybe also other health technologies to allow for comparison and lower the risk to randomise to placebo. There are also other important issues such as the **access to experimental medicines at the end of the clinical trial** for the trial participants which is a very frequent issue and discussed by many patient advocates. There are on-treatment studies or longer-term registries where a standard/guideline might be missing. Another area in need of consideration is the **standardisation of data collection in compassionate use** – this is real word data which often varies in quality and is not systematically collected.

In summary, the third revision of ICH E6 is very welcomed and patient organisations could certainly contribute, starting with interventional clinical trials and then moving into additional considerations for non-traditional interventional clinical trials. This is critical as there is a need to explain all these changes to patient organisations constituencies and all patients in general. We could propose a standard on how to engage with patients to discuss the aspects of clinical trials; this is sometimes done by the sponsors where they set their own advisory group, sometimes it is the patient community that sets a community advisory board. There are different models, different rules, different guidance and this is a **unique opportunity to define a global standard on patient engagement in clinical trials**.

Marco Greco (EPF) shared more patient perspectives (see presentation). As remarked by other speakers, the need for renovation arises from changes in the environment of clinical research – including impact of new technologies – big data, new trial designs, proportionate risk-based approach, use of digital tools. Marco underlined that the **fundamental ethical principles should be respected while adapting to new realities** and emphasised that the patient role has evolved since guidelines were last revised with the current revision being an opportunity to contribute to more patient-centred trials. In particular, important areas to consider include **informed consent** and **patient involvement**.

Clinical trials, and the scope of ICH guidelines, address one piece in the puzzle of research and development of new therapies and patient involvement needs be understood holistically in that wider picture. In the field of clinical trials, patients can be involved at the time of defining the clinical question/problem, in the trial design, in patient recruitment (e.g. providing information on clinical trials, advertising trials), and in aspects of the trial management (e.g. consent, patient information leaflet, trial adherence). It is recognised that the impact of patient involvement is greater, the earlier it happens.

One **critical opportunity is to consider guidance on informed consent** and the opportunities and potential caveats of **using innovative models for informed consent** via online, interactive tools or any e-concept. These have the potential to really empower the patient who need to decide whether to participate in a clinical trial. It is largely understood today that huge piles of legal documentation are not in the patient's interest. Nevertheless, informed consent is still of varying quality, often seen as a legal tick box for protecting the researcher rather than the patient. The paradox is that this kind of imbalanced informed consent may face in the future issues of legal consistency and validity. Let us revise them not only for patients but with patients. There is a **need for guidance on adequate and timely procedures for how patients can confirm they understood the information and agree to participate in the trial**. Aspects to consider include how dynamic and multi-tiered information can

be given to counsel people as well as the needs of specific patient populations and individuals such as those with limited capacity to consent.

Other questions to be raised include how to evaluate the quality of the information in the informed consent and the process itself. There are increasingly cases where **patient organisations have developed or co-developed informed consent forms and contributed to the process**. These recent good practice examples should inform the overall revision ICH is undertaking. The protection of data is and must remain a priority. As more and more we will be using wearables, data collection strategies need to be more transparent; the potential of this items is enormous, but the risk is under the same parameter. The informed consent has to be crystal clear when it comes to the electronic data collection as it is too easy to collect extra data (e.g. to access the individual's cardiovascular risk even if it is not important for the trial *per se*) and patients need to understand where will the information go, where will it be circulated, how will it be circulated.

There is a need to **create a new section to address aspects of patient involvement** as patients provide the data, take the risks and benefit from the results. Too many trials address research questions or measure outcomes that are not what matters most for patients. It is well known today that patient involvement contributes to clinical trial legitimacy, transparency and accountability of research. Ultimately, patient involvement leads to better, more relevant research results.

Furthermore, **alignment of innovation with real unmet needs** is absolutely required and impacts design of trials, where endpoints must be relevant and focus on quality of life and patient relevant outcome measures. Design should **consider patient priorities in terms of benefits and risks**, and inclusion and exclusion criteria must reflect "real world". Better **quality of information material** is paramount and there is a need for trial's practical arrangements to be **less burdensome** promoting fewer drop-outs and better adherence, ultimately resulting in better data. Ethical aspects of the trial need to be brought into the picture and there must be room for challenging researchers' assumptions, adding new knowledge, and further disseminating results.

ICH can **draw from current good practices** and take inspiration and guidance from resources developed by PARADIGM and EUPATI as well as others (e.g. PFMD, Transcelerate) and potentially aligning with the expected **global guidance on patient involvement** to be published by CIOMS Working Group XI.

In relation to **terminology**, there are terms in need of updating. For example, moving away from "subjects" towards "participants" or "volunteers". Of note is also the need for **training in GCP**, including how to involve patients.

In conclusion, the ICH E6 guideline does not cover all aspects of research or patient involvement in overall research. However, it is a very influential piece in the growing puzzle of research and development and therefore it is vital to get it right and ensure patients are involved correctly and efficiently.

3.2 HCPWP perspectives

Martin Landray (ESC) shared experiences, expectations and aspirations for the ICH E6(R3) revision from a clinical trialist perspective (see presentation).

Martin emphasised that the **overall aim is to deliver good evidence from clinical trials to improve clinical care**. Sometimes, the obsession on how to create the perfect trial leads to a trial that is never being done or being too small or too restrictive in one way or another to inform future care and ending as an overall disservice to public health and individual patients. It is therefore key to think about what we are trying to achieve with the guidelines, and it is **essential to focus on the**

3. Patients, consumers, healthcare professionals and clinical researchers Perspectives

"Why" and not on who, what, where, or how. A possible structure to consider for the guidance would encompass three sections: guiding principles; approach to quality; and operational considerations. Fundamentally there are **two guiding principles: protect the rights, safety and well-being of study participants and ensure the reliability of the results (for benefit of future patients)**. The focus should be on appropriate ethics approval, safe administration and monitoring of investigational medicines, safe study procedures and investigations, and on detecting and quantifying the efficacy and safety of treatment. Everything else needs to be considered under one of those two principles or both. These should be a constant reference point throughout the rest of the guidance. The **approach to quality needs to remain quality by design (QbD)** as already included in E6 last addendum however this needs to be specified in the protocol. And needs to be **proportionate and focussed on what is special in the clinical trial by comparison to usual clinical care**. Quality starts with a well-articulated protocol and quality management should focus on delivering the protocol, with monitoring highlighting issues and enabling improvement. "Quality" in clinical trials is defined as the absence of errors that matter to decision making i.e. errors which have a meaningful impact on the safety of trial participants or the credibility of the results (and thereby the care of future patients).

Operational considerations are already highlighted on the current E6 Principles and CTTI QbD Principles Document, and apart from some aspects that can still be refined, are by large well-defined. Martin provided some other examples of what is already good in the current guideline and that promote a proportionate approach to trial quality and some examples of what creates confusion and caution.

Martin also elaborated on some suggestions to what needs improving in GCP guidelines to deliver reliable results, remarking that reliable answers do not require "perfect" data (if such a thing exists). Focus should rather be on highlighting **key issues that influence results**, such as allocation concealment and randomisation, adherence to follow-up / "withdrawal", ascertainment of outcomes, inappropriate unblinding of results. There should also be a **rational approach to safety monitoring** (with emphasis on randomised comparisons rather than crude "relatedness" assessments). More can also be done to **ensure definitions are clear and consistent**. In relation to aspects that can be improved in the guidelines to ensure participant well-being, it is relevant to recognise that many trials pose only a minimal additional risk to participant safety compared to normal clinical practice (tailor consent, data collection, and clinical monitoring accordingly). Another important matter is to have **proportionate consent processes that inform participants** (rather than collecting paper or protecting the institution and to consider major safety issues (from medicine or investigations), and appropriate ways to avoid, mitigate, or monitor (consider what is different from routine care). Fostering innovation will require to emphasise the principles and considerations, allow trialists to determine efficient and effective solutions, **discourage excessive, defensive practice** (e.g. oversight) and recognise that 'essential documents' are not always essential or documents.

The EU Clinical Trials Regulation (536/2014) has much to like as it accommodates "low-intervention clinical trial" and risk-proportionate processes (including data collection, monitoring, AE reporting, trial master file), deals appropriately with consent in different circumstances (e.g. incapacity, minors, pregnancy, emergencies), emphasises need for suitable facilities and appropriately trained staff, acknowledges and accommodates co-sponsorship (provided well documented), and acknowledges that principal investigators are responsible for ensuring compliance of a clinical trial at their site but may assign tasks among members of the team.

The guideline must undergo **careful drafting keeping in mind its thoughtful application**. It is fully recognised that many historical complaints about GCP are as much caused by excessive, unthinking application or over-interpretation as by poor drafting of the guidelines themselves. It is thus critical that the drafting of guidelines **includes the full range of stakeholders who will be involved in**

their subsequent use.

In summary, the future for GCP Guidelines resides in writing guidelines that will stand the test of time. The aim is to have rational and proportionate GCP guidelines which enable timely, affordable and high-quality assessment of the benefits and harms of health interventions (and in the specific case of E6, medicines). They must be based on key scientific and ethical principles – focused on issues that materially influence the well-being of trial participants and reliability of the results. They should be clear, concise, consistent and proportionate – recognise the risks associated with usual clinical practice and lack of reliable evidence on treatment effects. The guidelines should be co-developed through an Open Regulatory Science approach – involving regulators, funders, commercial and academic trialists, clinicians, patients and public. E6 renovation needs to be forward looking in order to foster innovation in health interventions and trial methods – e.g. take advantage of digital technology, data analytics and genomics. Finally, the final guidance must be broadly applicable, widely adopted and durable – across disease areas, intervention types, development phases, trial designs, geographies and time.

Martin Dreyling (EHA) gave a perspective on the impact of ICH E6 from a clinical investigator viewpoint (see presentation). Martin underlined the importance of this guideline as it sets out the foundations for good clinical practice (GCP). In essence, **GCP should be patient-centred and investigator-friendly** and therefore the initiative to complete the feedback loop with the earlier involvement of patients and clinical researchers and avoid some of the shortcomings of prior versions of ICH E6(R3) is welcomed.

The European Haematology Association (EHA) is committed to increasing patient safety and reducing bureaucracy in clinical trials and thus through a bottom-up initiative, is working with key stakeholders to find solutions to the **challenges posed by certain bureaucratic obstacles in clinical trials**, mainly: excessive safety reporting, comprehensibility of informed consent forms, and regulatory ambiguity.

In terms of safety reporting it is extremely important this is done by medical experts and that the focus is on collecting the information which is in fact relevant for the study. Otherwise the risk is that the important safety information is hidden in the overwhelming amount of non-relevant information collected. There is a need to simplify and standardize safety reporting forms and prevent sponsors from making their own reports. In addition, the process should be formulated as a 'friendly request' with no unnecessary steps or formal signatures and inspiration could be drawn from the Australasian experience. A clear definition of what a serious adverse event (SAE) is, with a grading that allows to distinguish what is serious and what is severe is necessary. Without serious and effective modifications, it will be impossible to **reduce the amount of work due to overinterpretation of SAEs**.

In relation to **informed consent forms** (ICFs), these **should be short and understandable**, as stated in ICH E6. However, the list of items in 4.8.1 is excessively long. A two-step document with 1 or 2-page summary plus explanations, including biologic assessment, could be helpful. Implementing improvements in ICFs can only be done by **involving patient organisations in the writing of these forms**.

In what concerns sponsors and clinical research organisations (CROs), ICH E6 rightly recommends to "avoid unnecessary complexity, procedures, and data collection". What is lacking is **clear guidance for** implementation and stating what is 'unnecessary complexity', **what is essential and what is not, what is mandatory and what is optional**. This is critical as what happens in reality is that prerequisites are extended due to safety but also financial motivations and what could be a fairly simple protocol study ends up as a very long document with 30 additional documents attached. The current thinking towards a **risk-based approach is welcomed** as not all studies are the same and

requirements therefore could be applied in a more proportionate way depending on the type of study. For example, a first-in-man trial would require a full safety process, but a therapy optimisation study may not need the same exact level. Furthermore, the **transfer of all duties to the CRO by the sponsor is a risk**. Safety-related responsibilities should not be transferred and should be agreed between the sponsor and the investigator.

In summary, the **critical element will remain on how to implement the ICH recommendations**. Overinterpretation of GCP guidelines, mainly by CROs, perverts the initial aim of optimising patient safety. Therefore, more clarity about how, who, where, when to implement these recommendations would be helpful. Perhaps a solution could be to have abbreviated guidelines, alongside the revised full version.

3.3 ECRIN

Jacques Demotes-Mainard (ECRIN) elaborated on four main challenges faced by the non-commercial structures in terms of new design of clinical trials and data use. These cover personalised medicine research, secondary use of data, complex trials, and risk-based approach (see presentation).

The European Clinical Research Infrastructure Network (ECRIN) is a non-profit organisation whose mission is to support multinational trials in Europe. ECRIN supports any type of trial falling between the spectrum of two categories of trials: registration trials/ repurposing trials and comparative trials. The first are centred on the medicine and they address the question raised by the regulatory medicines agencies on whether a medicine deserves a marketing authorisation or an extension of the marketing authorisation. On the other hand, comparative trials are a group of trials that are meeting the expectations of the health technology assessment (HTA) bodies and addressing the questions raised by HTA bodies on what is the best treatment option or the best treatment strategy for a specific disease/condition or for a group of patients. There are also trials that can address both types of questions.

In relation to **personalised medicine research**, ECRIN is currently coordinating the EU-funded project *PERsonalised MedicIne trials* (PERMIT), started in January 2020. The project aims to address how to establish methodological standards not only for the trial but for the whole package of personalised medicine research programmes.

Such research programmes usually start with a stratification cohort where clinical data together with multi-omics data are collected (either retrospective or prospective) and then these data are used to feed machine learning algorithms that determine whether there are multiple homogeneous clusters of patients. Then, there is a second cohort for validation and based on this clustering a multi-arm trial is run to test different treatment options in each of the sub-groups. The problem is not so much with the multi-arm trial but rather with the reproducibility of the data and of the algorithm that generates the clustering of patients. This is where we would like to have more guidance, i.e. is there a need for a C€ label for the multi-omics analysis used to stratify the patients?; do we have to have a quality control and traceability of the data?; what are the mechanisms that need to be in place to validate the machine learning stratification?. These questions will be addressed by the PERMIT project but this is something that must involve regulators and we have among others, the EMA as partners, the Clinical Trial Facilitation Group (CTFG) and EUNetHTA. It is very important to answer these questions as currently regulators face difficulties when they have to accept the quality and the reproducibility of the outcome of the trials.

Secondary use of data is another concern. Currently there are some pilot studies using registries and cohorts, i.e. research data for research purposes. In the future it will certainly be also possible to use electronic health records (EHR) from hospitals to run clinical trials. However, these raise several problems including the harmonisation of data standards. ICH could explore making a specific recommendation for a standard to facilitate the combination of data from multiple cohorts, multiple registries, multiple hospitals for running clinical trials. The standard for clinical trial data CDISC is becoming the standard for the application to the FDA (USA) and PMDA (Japan), however, should we go

for a global clinical standard or is it possible to cope with the diversity of data standards? Furthermore, it would be important for the research community to define what methods should be used to ensure data quality and traceability, e.g. when EHR are used for secondary use to feed the case report forms (CRF) of clinical trials.

Regarding the data protection regulation, this is a problem specially for data sharing. The GDPR in Europe is a very stringent regulation which is different from the HIPAA rule in the USA. For example, it is possible to have a dataset considered as deidentified from a HIPAA perspective but pseudonymised data require an informed consent in a secured environment and controlled access from a GDPR perspective. This is also an element of disharmony that could be potentially tackled by ICH.

The broad consent for secondary use / data sharing is another important issue. Some national regulations tend to have it based on the objective of why the data would be reused; but the important question is not the why but the how – how will data be shared, what are the security procedures, and what is the controlled access that will ensure compliance with the data protection regulation.

Jacques illustrated the benefits of using research data for research purpose with the TASTE trial, run in 2013 as the first randomised clinical trial based on registry data. This made it possible to have 6000 patients with myocardial infarction over two years at a very low cost per patient.

The third challenge involves **complex trials, and especially adaptive platform trials**. They are very complex and interestingly they can both be used for marketing authorisation and for comparative effectiveness. In theory they can be used to compare to standard of care and get a marketing authorisation but can also be used to compare head to head different treatments to answer the questions raised by the HTA bodies on what the best treatment or the most cost-effective treatment is for a specific disease/condition. These again raise several problems, namely related with data management as sponsors, specially the industry, want to have compartmentation of the data management. The statistical methods may also raise some questions, with for example, some competent authorities reluctant to use Bayesian analysis. The concept of sponsor and co-sponsor is a prominent issue in Europe. In other world regions is possible to have one sponsor per arm but the EU regulation states that only a singly sponsor is foreseen. In terms of data sharing the EU regulation foresees that data on the control arm should be also shared but in the case of a multi-arm trial with a common control group again there are questions raised for which further guidance is needed in order to make it possible to handle these complex trials in the European context.

Finally, in relation to **risk-based trial management and oversight**. In 2013 the OECD released a recommendation on the governance of clinical trials with two major objectives: 1) the implementation of risk-based provisions in the oversight and management methodology for clinical trials; and 2) their harmonisation, i.e. alignment of regulatory requirements for clinical trials worldwide to facilitate trans-national clinical research. Whilst the first objective has seen interesting progress in many of the world regions it is not yet completely achieved as the implementation of such provisions is done according to different principles. This means the second objective was not really met; one of the disappointments is that no worldwide alignment was achieved to fit the distinction between an investigational new drug (IND) and a non-IND trial with the boundaries between a low-intervention trial and a regular trial as in the European legislation. In Europe this leaves some of the repurposing trials in a complex situation. This is something that could also be explored.

3.4 EORTC

Denis Lacombe (EORTC) gave the perspective from a non-profit cancer clinical research organisation (see presentation). Denis started with some high-level remarks, pointing out clinical research is a component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health. Therefore, having GCP limited to regulatory and particularly to drug trials is a very reductive approach which does not take into account the full research environment. The **revision should be approached as a patient topic and not as a medicine issue** and cover the entire continuum from (early) drug development into applied

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clinical trials. The GCP revision is an opportunity to re-engineer a holistic continuum of research from innovation into therapeutic strategy instead of separating the two. Such separation will perpetuate a two-tiered research where innovation is of high-standard but completely detached from reality.

Science and methodology evolve very fast and living with a static document is no longer a solution. **ICH E6 needs to become a guideline which is agile, proportionate, risk based and evolutive**. The ultimate goal is to constantly facilitate adaptation to changing environments, new types of trials collecting multidimensional data, and capable of reaching all patients. Denis challenged the ICH E6(R3) definition of traditional versus non-traditional clinical trials – what is a traditional clinical? The regulatory industry model should not drive the approach but rather the diversity of clinical trials and of clinical questions and there is a need to adapt to the question and the environment. Also to be challenged is the approach to develop annexes 1 and 2 in a sequential way over a period of months/years; it is suggested to start with the pragmatic aspects and then look into the complex aspects but to look at it as a whole and at once.

In a transformative society, the actors in the clinical research field should "unlearn" what they have done, so that they can learn how to do things differently and create completely new concepts. The idea is to reach a process to efficiently perform widely applicable clinical research in the best interest of therapeutic progress while preserving patient interests and rights.

Some areas of attention for this revision include the need to place all stakeholders around the table at ICH level, including academia and patients. The focus should be on using available resources to **raise quality and not documentation**. Equally important is to elevate the process of patient informed consent, with the possibility to opt out; to have a one time-consent supported by a short and focused document which can adapt to multifaceted protocols; to focus on what is new and deserves attention, not what is already known and where priority is given to qualitative over quantitative and variable information. There is a need to **go back to the basics of what is the intention of informed consent**. Another critical area is the **way how protocol amendments are to be done**. This should allow for group changes over time when possible and only process live what impacts the investigational part of the protocol and thus the patient.

Furthermore, all will need to be put through the angle of **digital transformation to serve the process** with a view to provide clarity on what are the required documents to upload, encourage remote and proportionate monitoring, and reduce bureaucracy. This would involve limiting data collection to what is really needed, including decreasing the amount of reporting of serious adverse events particularly if these are related to already tested medicines, and adapt definitions to the reality where multiple principal investigators can reach to patients where they are.

In conclusion, if proportionality is not applied European patients will be deprived from therapeutic progress.

4. Discussion

Several questions and remarks were addressed during the discussion period, which are summarised in this section.

- Lack of debate and harmonisation around pecuniary compensation of patients who accepted to be enrolled in clinical trials - this is a topic quite open to regional sensitivities in the areas of ethics discussion and probably not something ICH will harmonize *per se* across the regions but rather that it would be maintained that such matter should be considered by the Ethics Committees involved.
- Need to structurally involve ethics committees in the writing of the new GCP guideline in order to bring their input into informed consent, protocol review, increased evidence-based decisions, wider

representation of population sub-groups, and look at what really adds value and is proportionate with regard to input, human resources, money, time, etc. – in order to further discuss aspects falling under ethical considerations, the ICH EWG will be interacting very closely with the Clinical Trials Expert Group (CTEG), which brings together national competent authorities as well as national experts from ethic committees across the EU.

- Need to enable larger clinical trials to bring in a wider participant population in the trials as much as possible was acknowledged.
- Proportionality and added value in relation to monitoring and source data verification (SDV) – the process of cross-referencing data recorded in a case-report form to the original source information – is one of the areas most people are pointing as in need of revision. ICH E6(R2) already put more emphasis on centralised monitoring in acknowledgement that onsite monitoring and SDV is not the only way to ensure data quality. The risk-based approach which was part of ICH E6(R2) pointed into the direction of not focusing only on onsite monitoring but also using all the other possibilities for data review in a smart way, making use of all new available technologies (e.g. using remote monitoring). For some new data sources such as patient reported outcomes and patient diaries, the reported data are the source data at the same time and although there will be a need to have a review and metareview of the data this does not require SDV per se. In summary, ICH E6(R2) already allows for making that switch from onsite monitoring and SDV to using other tools.
- How does ICH interact with international patient and healthcare professional groups and regional fora?

  There are currently no global patient or healthcare professional organistions as observers in ICH (with possibility to participate in assembly meetings and request to appoint experts in expert working groups); umbrella organisations are the most likely to be eligible and details on eligibility criteria and how to apply can be found on the ICH website. Until such observers join ICH, it is encouraged that organisations contact their counterparts in other regions as well as encourage potential global organisations to apply to become ICH observers; in either case, ICH will continue its regional reach out activities to ensure regional and cultural differences can be taken into account.
- Will the scope of the revision only cover medicines, or will it address other areas including devices? What is the interaction between ICH and IMDRF?

  The scope of ICH includes clinical trials of medicines. These may include devices if used as part of the administration or as a treatment arm. However, the area of device trials as such is out of ICH scope of discussion and regulated quite differently in different parts of the world. The interaction with IMDRF is handled by the EC unit dealing with medical devices.
- Making consent simpler – while clear and robust – is a key and increasing challenge. What progress has been made in piloting less complex consent processes towards aiming for as high as possible recruitment in future studies?

  Different organisations, including TransCelerate with its eConsent initiative, are looking at the consent process and how to digitalise it and capture different ways in which people read and visualise information.

  Although there have been several scientific advice requests on electronic informed consent, these have not yet been seen during inspections. This could point towards some hesitation in their implementation but also to the need for further guidance. In parallel, the ICH GCP principle on informed consent is being reflected upon as its wording states that an informed consent, from each

participant, is needed prior to clinical trial participation and this is not reflective of all situations in clinical trials going forward (e.g. emergency trials or the special approaches for cohort trials). Discussion is therefore ongoing on how to reflect alternatives into the ICH GCP principle.

- There is a need to further elaborate on the concept to involve more than one investigator and/or institutions in the treatment of a single patient and how the collaboration could look like. In the oncology field, there are ever more specific clinical situations where patients do not necessarily need or cannot reach the big cancer centres (e.g. treatments are more oral; there may be more aggressive side effects; patient quality of life; adherence to protocol). EORTC is increasingly working with recruiting centres and treatment centres to enable patients accessing clinical trials, e.g. through a central organisation that works with a network of sites, closer to their home. In these cases, patients can be taken in charge for the same clinical trial through different institutions. In addition, there is also the issue of multiple investigators specially when working across multiple tumour types or in very pragmatic trials where, for instance, a radiation oncologist, a surgeon and a medical oncologist are required in a sequence of treatment to be addressed in the clinical trial. The benefits and the need for having more than one investigator is acknowledged but more clarity is required from a very practical viewpoint on who at the end has the oversight about the treatment decision and how investigators located in different institutions can collaborate (e.g. share medical exams and documents). This is possible in a scenario where electronic health records are accessible from multiple points and work is developed with the support of multidisciplinary boards. In such scenario, not all expertise is necessarily in a single institution and there are people giving advice and reviewing MRI imaging located in other institutions. In this type of model, a single patient can benefit from cross-expertise of different types of doctors that they may need. This however might be very specific to oncology. Also important to note is the pattern of relapse of oncologic patients; i.e., when a patient relapse they may or may not be at the institution where they received the treatment and this continuum of care is very important to understand how the treatment is working and what are the patient's escape mechanisms. With all this in mind, it might be critical to completely reinvent the solution for ICH GCP rather than adapting old mechanisms which will not meet the needs.
- Need to support training for patients and use the EMA as a platform for training patients on clinical research and clinical trials and increasing knowledge about benefit and risk of clinical research. The revision of ICH E6 is an opportunity to properly explain processes and any new concepts introduced. Training and awareness can reinforce and facilitate implementation and understanding of the principles included in the guidance.
- Importance of including patients in the whole process of trial design was underlined together with the need to make sure that all information/explanations going to patients are reviewed by patients and appropriately written in lay-language.
- What is the thinking behind increasing participation of elderly patients in clinical trials, including the use of new technologies?

  The key will reside on quality by design to ensure that the protocol is taking into account the patient population that the trial is including. It is also the principal investigator responsibility to make sure that it is feasible for the patient to be included. The EU GCP Inspectors Working Group (EU GCP IWG) is currently drafting guidance for electronic systems in clinical trials and one of the things being emphasised is that already at the point of defining such electronic systems there is a need to ensure potential participants will not be excluded on the basis of the electronic systems used. Unfortunately, there is still often the case where inspectors are seeing systems which are not well designed for the patient populations they are intended to be used for. It all comes back to the

4. Discussion

simple protocol design and the inclusion/exclusion criteria and we still see a systematic exclusion of more than 65 years old (and this applies to other populations as well). This needs to be rethought and is currently being discussed within the ICH E8 general considerations on clinical trials. There is also a broader discussion taking place amongst regulators to better enable that these groups can be participants in clinical trials and have data on the use of medicines in these populations. Trials need to be well designed and have a well-articulated protocol which is rethought and refocused each time a new trial is designed. It must be also acknowledged that more and more, the older generations will have grown up in an electronic environment and this should not be underestimated.

5. Next steps

Juan Garcia Burgos and Fergus Sweeney wrap up the discussion pointing to the very rich input received from a wide range of presenters which has contributed to workshop participants, including ICH EWG members, gathering new information and a better understanding of the challenges faced by the revision of the guidance.

In summary, the key areas highlighted throughout the workshop that should be addressed included:

- Patient involvement, openness to eConsent, decentralised trials and the need for consent to be informative; this will enable larger trials which will bring in broader patient populations;
- Run clinical trials to generate results and assist in decision-making; for that reliability of results is key to protecting participants themselves and the patients who in the future will be using the medicine; this all rests on a well-designed and well-articulated protocol;
- Focus on what is really important to the quality of the trial and participants' protection and avoid complexity and overinterpretation.

The input received will support the re-write of the GCP in a way which is more proportionate and which guards against unnecessary overinterpretation. However, change management will be key. We need to unlearn old habits and approaches and to learn new ones which support trial participants and the collection of information that is reliable for decision making and relevant for patients.

In order to implement the engagement proposal ICH will ask for nomination of representatives from different world regions to interact with the ICH E6(R3) GCP EWG and then the EWG will establish a process for interacting through face-to-face meetings if and when possible in the context of the COVID-19 crisis and through teleconferences. As the drafting of the guideline progresses, EMA will come back to PCWP and HCPWP for regular updates.