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Executive summary

The opportunities and challenges presented by complex clinical trials (CCTs) were reviewed in a two-day on-line multi-stakeholder workshop on October 5-6 2021, with wide attendance from across the international healthcare community, and assiduous attention to the distinct perspectives that each stakeholder brought.

The workshop delivered detailed analysis of crucial aspects of the design, conduct and regulation of CCTs, matched with plenary sessions that contextualised the discussions and outlined constructive possible ways ahead. **Key recommendations from the workshop appear below.**

A scene-setting introduction by regulators from the EU and USA highlighted moves on both sides of the Atlantic as **regulators begin adjusting to the potential opportunities that CCTs** can offer in faster or more targeted drug development – although with due caution over the quality and relevance of evidence, and without comment on the implications for health technology assessment. Alongside, an array of current and recent EU-funded projects exploring complex trials was presented. **An outline of the opportunities and challenges offered by CCTs appears in Annex 1.**

This was followed by a presentation of **CCT-related priorities and expectations from patients, regulators, ethics committees, Health Technology Assessment bodies (HTAbs), sponsors and investigators**, establishing a base-line for the subsequent examination of methodologies, mechanisms and metrics.

Six break-out sessions focused on specific areas of challenge in CCTs: **master protocols, regulatory processes, patient involvement, historical controls and adaptive features, operational aspects, and education and training.** Annex 2 to this report includes detailed accounts of each of these.

A concluding plenary session on the principal outputs and **possible future actions** featured views from EU and US regulators, the European Commission, ethics committees, patients, HTA bodies, industry, and non-governmental organisations engaged in investigation.

This was **not just another webinar**. More than 400 people registered, with an audience of 288 watching live the first day and 184 on the second day. The discussions took place against a background of **the rapidly-evolving broader context** in science and technology, in the regulatory framework, and in health policy.

The key themes that emerged included the current limited awareness or understanding of CCTs, the need for collaboration - especially greater involvement of patients, and the still-unexplored implications of CCTs for HTAbs and payers.

Key recommendations

Key recommendations to emerge from the discussions included…

- change from a drug-centric to a systematic patient-centric approach to trial design
- seek wide consensus on definitions and terminology to facilitate wider understanding
- ensure early formulation of the trial objective, end-points and key design aspects, so as to address the research question posed, identify what data will be needed, and explain the process clearly
- ensure early engagement with patients, regulators and HTAbs in trial design, and consistently throughout trial execution
- maximise learning among all stakeholders, with experience-based common templates; establish agile and comprehensive collaboration and neutral platforms for knowledge-sharing and pilots, including at global level
- encourage training and alignment on trial-design principles across regulatory agencies, HTA bodies and other stakeholders
- ensure early agreement on clear accountability, governance, liability and IP protection in multi-sponsor studies
- clearly distinguish advice, collaborative discussion, and approval activities in regulatory discussions
- explore CCT opportunities in rare disease and paediatric trials
- explore CCT opportunities in confirmatory settings in multi-sponsor studies

Stakeholders' views

The views that emerged from key stakeholder groups during the workshop can be summarised as follows:

- **Regulators'** interest in the merits of CCTs is growing, as seen in the inception of an FDA pilot, EU plans for sweeping legislative reform that explicitly mention support for innovative trial designs, the review by the Clinical Trials Facilitation and Coordination Group (CTFG) of guidance on CCTs, or the transformative priorities of EMA. Regulators are exploring options as their perspective on drug development moves increasingly towards value for the patient-end user and the use of patient relevant outcome measures. *"We remain patient-focused in everything we do,"* said one EMA representative. But with the inevitable caution of their discipline, regulators reminded the workshop of the demands of existing regulation ("*The European regulatory framework requires that each clinical trial is assessed individually…"* with a bottom line that *"because increasing complexity implies increasing risk, adequate arrangements must be made for risk mitigation"*). Regulators strongly encouraged sponsors to communicate early, to take account of the guidance that is available, to plan effectively, and to ensure that all elements of the trial design reflect the overarching scientific concept. Sponsors should also be ready to fully justify the selection of a CCT approach rather than more classical/standard trials. There is also recognition among regulators that without more alignment among themselves there are risks of duplication or even contradiction, and they also indicated support for the idea of collaborative multi-stakeholder platforms to facilitate interaction and learning – but with a careful line between advisory discussions and collaborative discussions, and with respect for the mandates and responsibilities of each stakeholder group.

- **Clinical and academic researchers** are eager to explore new tools that can support their use of the rapidly growing understanding of disease and treatment. They are key drivers in the move to increased use of CCTs, as university hospitals dealing with very complex situations are seeking new approaches to trials – particularly for cancer. But they are confronted not only with the scientific challenges of evolving new approaches and with the intrinsic complexity of the diseases they are learning to treat better, but also with the rigidity or hesitations that still condition some traditional regulatory attitudes towards novel trial approaches. One researcher recounted how it was only through an innovative basket trial design using a suite of molecular matching trials from industry and from academia that it was possible to resolve a difficulty in a cancer precision medicine program for paediatric patients in Europe. But she noted the challenges this raised in coordination, particularly since six countries – and six regulatory authorities – were involved. Simplifying the setup was seen as a way to allow a still-clearer focus.

- **Industry** wants to deploy mechanisms that optimise drug development, particularly for unmet needs – and CCT can help inform the best possible decision at the earliest

time and in the most efficient manner. Leveraging innovative methodologies like adaptive features in clinical trials compared to traditional designs offers the chance of accelerating trials with high probability of success (PoS) and stopping trials with a low PoS earlier, thus making it possible to avoid wasted efforts. The reduction in the sample size or timeline does not necessarily imply greater risk, and can mean a lower probability of making the wrong decision in drug development. But the lack of awareness and understanding among stakeholders and even within the industry is a challenge, exacerbated by a lack of regulatory guidance on many aspects of CCTs. And although the resounding ask is for a collaborative regulatory process, there are only limited mechanisms – such as industry and academia efforts in the IMI EU-Pearl programme - to bring stakeholders together to develop common understanding, which is still more of a challenge for global development programmes, on which greater convergence by regulators of innovative methodologies is vital. There are scientific challenges in adapting a protocol while preserving the overarching hypothesis, accentuated by operational challenges in foreseeing all possible modifications and adaptations at the time of trial design and conduct. There are variations in standard of care both over time and in different regions and countries, exacerbated by varying and sometimes inconsistent requirements and expectations from different regulatory and HTAbs within and between countries.

- **Patients** want timely access to innovative and transformative therapies. *"Accelerating the adoption of complex clinical trials in Europe and beyond is vital to us because we patients desperately need innovative treatments. We urgently need new approaches to how we accelerate learning. At the current rate it will take us another 200 years to find cures for all 200 cancers, not to speak of more than 5000 rare diseases and many other chronic conditions which are genuinely severe. We've been calling for innovative trial design for so long"*, said one patient representative. But while enthusiastic about the prospects for new treatments, patients are also keen to ensure their views and interests are fully respected in trial design and treatment. *"We need to have patients involved in research and trials, and funding for projects to improve patient engagement and create acceptance of patient involvement in research,"* said another. Patients are principally concerned about the risk-benefit of a trial. *"With all the best methodologies and smart designs, complex trials won't work if patients don't want to join these technical studies or drop out halfway through because they don't understand what they're in."* CCTs must be designed so that patients are comfortable joining – and that needs more than awareness campaigns or joint recruitment efforts. It means the trial design must recognise what patients need and expect, and patient involvement must run from the planning stage to the end of the trial. It means a different way of looking at inclusion and exclusion criteria, more awareness of the effects of medication, and validated ways of measuring effects. It is essential to ensure patient engagement is genuine, and more than a tick in a box. And in addition to risk and benefit, it is important to maximise ease of use, adequate information, and availability and access.

- **Research ethics committees (RECs)** are conscious of the risks of being overwhelmed by additional – and more complex – demands on their largely voluntary membership, raising questions of resources and training. RECs need to convey new knowledge to their members and raise awareness. Protocols are complex and long, sometimes with references to documents that are not readily available. The scrutiny must include protocol amendments, sample size, statistical analysis, trial design, informed consent documents – which are often too long, the quality of investigators and facilities, and insurance issues. Clearly defined stopping rules and rules for discontinuation are also essential, as are details on responsible data safety management boards. RECs need to see indications of any change in the risk benefit and changes in the standard of care, but in general amendments should be kept to the minimum. In particular, RECs feel the need for expert input from statisticians, an asset not always easily available, particularly for smaller provincial ethics committees. Even where university RECs are familiar with the concept of CCT designs, it is often impossible to meet the tight timelines for assessment. RECs would like their fees for reviewing CCTs to be revised, better taking into account the complexity of the initial clinical trial application or substantial amendment dossier, and hence the review workload. Underlying all the detailed comments is the generalisation that RECs should be involved in the discussion of novel concepts at the earliest stage. And there is a strong call from patient representatives for a place on RECs to ensure adequate ethical evaluation of CCTs. Of note, article 9.3 3 of the EU CT Regulation stipulates that "… At least one layperson shall participate in the assessment of Clinical Trial Applications…".

- **Health Technology Assessment bodies (HTAbs)** are hesitant, even sceptical, and mistrustful, over what they see as a focus on efficacy that omits due concern for the relative efficacy that it is their role to gauge. Further discussion is seen as urgent with all stakeholders, but principally and initially with EMA and regulators. Beyond the mission of regulators to assess efficacy and safety, HTA bodies have to evaluate how (cost-)effective a product is, and whether it offers superiority – and a prominent HTA representative stressed his view that most CCT definitions and discussions ignore the issue of relative effectiveness. Consequently, there is scepticism about CCTs and a lack of trust from HTA bodies and payers, particularly about issues such as the reliability of data for external validation, effective metrics, or claims that trials without CCT designs would be impossible or unfeasible – rather than just inconvenient. There is a need for more information from independent bodies – rather than just the industry - about the new CCT designs, methods and concepts. While HTA bodies need to evolve to handle changing realities in product development, there is disappointment about their exclusion from discussions of the newer methods emerging, which would have benefited from earlier HTA bodies input on the increased use of innovative approaches, making it possible to incorporate also their needs. Involvement from the HTAb perspective from an early stage in the use of CCTs is essential: HTAb engagement in early scientific advice will be more meaningful if HTA bodies are involved in meetings where the methodological aspects are being discussed.

Key themes

A number of prominent themes emerged from the discussions and are detailed further below:

- the evolving context;
- the need for information and clarification;
- the need for wider collaboration;
- the need for reboot;
- the willingness to collaborate.

➢ The evolving context

There were repeated references to the avenues opening up in a changing background of advances in genomics, screening, biomarkers, artificial intelligence…. But equally significant were the shifts taking place in the regulatory framework, with the FDA pilot on complex trials, the imminent prospect of revised EU legislation on pharmaceuticals, complex innovative trial designs (CID), health data and diagnostics, the review by the CTFG of guidance on CCTs, or the transformative priorities of EMA. And wider health policy is in a state of flux in the EU, with moves towards closer collaboration among member states and growing recognition of the centrality of the patient. The situation was aptly summed up by an EMA representatives, who remarked on *"the increased understanding both of the genetics of the patients and of the genetics of the disease itself, and putting those two together we are facing the situation that the science has moved on and our historical traditional sort of clinical trial designs are no longer suited to answer those questions in the time that the patients are expecting to gain access to therapies".* And an FDA official observed: *"The ultimate goal is the wellbeing of the patient, and our role is to bring safe and effective products to patients in the most efficient way". "As a priority in EMA strategy,"* said one regulator. *"We are in the business of accelerating the adoption of complex clinical trials…" "There is a mandate for clinical trial innovation, spurred by the experience of the Covid pandemic,"* said an EMA official. *"The political will certainly exists in Europe for fostering this innovation in clinical trials."* At the same time, research is ongoing in evidence generation and clinical trials through public private partnerships, and ICH is working on harmonizing regulatory requirements and crucial guidelines supporting innovation in clinical trials. Another EMA representative spoke of *"an evolution in clinical evidence",* with a new Covid-induced focus on very large input from impactful multi-state studies that are data-driven, and regulatory processes that make it possible to integrate modern clinical evidence approaches, including raw data from clinical trials. The better use of real-world evidence, whether generated by industry, academia or regulators, will facilitate development of medicines, he said. *"The EMA work program will deliver real change which will support clinical evidence generation and that includes complex clinical trials."*

➢ The need for information and clarification

The need for information re-surfaced constantly during the discussions, and at all levels, from queries at the most basic issues such as CCT-related terminology or the scope and

implications of the EU's Clinical Trials Regulation (EU CTR 536/2014), through to uncertainties over Bayesian decision-making or Type 1 error, or the nature of a platform trial, or divergences between EU and FDA rules. Unanswered questions around: there is not even an agreed definition of CCTs. The roles or mandates or powers of each stakeholder in a rapidly evolving context could be enhanced by a clearer understanding. For instance, how should HTAbs evolve in relation to CCT, or how far should patients' views or assessments influence clinical trial authorisations? There are also questions over whether innovation for the sake of innovation may at times obscure the fundamental objective of improved care.

- **The need for wider collaboration**

In pursuit of the common interest of patient benefit, the importance of greater alignment across stakeholders was emphasised. This applies to the current divergences between regulatory systems – notably the US and the EU, but also to different approaches by regulators within Europe. It applies equally to different groups of stakeholders: HTAbs (and payers) remain largely outside the loop in discussions of CCT, observed their representatives at the workshop; the same point was made by representatives of ethics committees and patients. It is important that stakeholders have confidence that their perspectives are fully take account of, whether they are patients, RECs, regulators or HTAbs and payers.

- **The need for a reboot**

In some respects, the needs can be summarised as a 2020s reboot of traditional approaches to drug development. It amounts to a call for real engagement of patients, RECs and HTA bodies as stakeholders, fuller sponsor justification for choosing a CCT approach to a trial, and genuine early consultation among all stakeholders, as appropriate. It would build on current collaboration – such as in the Innovative Medicines Initiative – and the results that this has already shown in advancing trial design. Extending collaboration further, to all stakeholders, is the consequence of the recognition that appropriate collaboration may be more effective than competition in advancing patient benefit. As one EMA representative noted: *"There is no competitive advantage in keeping the knowledge to oneself".*

- **Willingness to collaborate**

Despite the multiplicity of distinct perspectives presented at the workshop, the refrain among stakeholders was a readiness to work together to seek and develop shared solutions. For instance, patients said: *"We all want to make complex trials and complex trial designs a reality. It's always so important that the different stakeholders get together."* FDA representatives welcomed the *"collaborative learning that we've been afforded through the disclosure"* in the FDA CID. Industry speakers looked forward to *"a brand-new flexible platform aimed at providing a modular trial network enabling European hospitals participation,"* paying tribute to the earlier work among experts from all stakeholder groups that lay behind the creation of the workshop. Growing interest in innovative design *"means collaboration to share learnings, patient involvement, training and education,"* said an EU representative, while a colleague remarked on the *"learning*

by all of us as a development community with the task of getting these innovative medicines into the hands of the doctors and the patients", and the merit therefore of working with stakeholders to promote CCTs: *"It will happen only if we get collaboration among all parties because of the extent of the challenges."* An industry representative urged *"listening to each other to try and find a solution together".* HTA body and ethics committee representatives expressed readiness to engage in dialogue. And an investigator offered thanks to patients and parents associations who had pushed for a particular trial, the national research and regulatory authorities that had supported it, and the pharmaceutical companies that had implemented it.

Conclusion

The workshop made clear not only where opportunities lie in CCT, but also where barriers still remain, often springing from the diverse interests and mandates of the participating stakeholders. Nonetheless, the consistent refrain among participants was a recognition of the potential, and a readiness to work together to seek and develop shared solutions. There is willingness to keep the momentum as expressed by all the stakeholders participating in the various breakout sessions, and an action plan agreed by all should be issued soon.

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Annex 1

Opportunities and challenges

The opportunities identified with CCTs include their potential for streamlining clinical development, using designs that allow shorter timelines and fewer trial subjects, offering the advantages of matching patients with the expected best available treatment. In contrast to traditional trial designs, where a single drug is tested in a single disease population in one clinical trial, CCTs employ a master protocol with a single infrastructure and trial design to simultaneously evaluate multiple drugs and/or disease populations in multiple sub-studies. The sub-studies may take different forms (umbrella, basket or platform trials), and adaptations are typically made throughout the trial in light of evidence generated. For instance in an adaptive platform trial with a single master protocol, new treatment groups can be added at any time, and candidate drugs that prove ineffective can be dropped – which makes patient enrolment easier, while patients benefit from an increased likelihood of being allocated a promising treatment. CCTs can provide a framework for the large-scale, multinational clinical trials that take advantage of linked data systems and innovative statistical methods, using a harmonised protocol and the collection of harmonised data across participating sites and countries to solve bottlenecks.

The challenges identified include general lack of awareness or understanding of complex clinical trials among key stakeholders, exacerbated by insufficient alignment of expectations and guidance. There are also resource issues among health authorities, and a general need to make adequate provision for education and training of stakeholders, particularly patients and members of RECs. More technical challenges include the management of complexity when several products, populations, trial sites, manufacturers and contract research organisations are involved; the management of modifications and substantial amendments to protocols; ethics - relating particularly to patient recruitment and informed consent; the timing of communication of results, so as to ensure due transparency on completed sub-studies without compromising the integrity of the overall CCT; ensuring independent study oversight; establishing insurance contracts; and resolving questions over Type I error in the Bayesian context for incorporation of historical data. Limitations of the application of the EU CT regulation are also a concern.

Annex 2

Breakout session reports

<u>Breakout session 1 - Design of Master Protocols: experience, key design challenges, and the future for multi-sponsor master protocols</u>

Master protocol designs are supporting innovative strategies for evidence generation, and this session made use of two case studies to illustrate some of the key challenges and sources of complexity when designing master protocols: Morpheus in oncology - a suite of Phase Ib studies designed to generate signal-seeking data across a wide scope of combination treatments, to support cross-indication learnings and identify combinations with transformational potential; and Piranga, an adaptive platform study Phase 2 design in infectious diseases. It was suggested that an adaptive data-driven platform design is more agile, contributes to de-risking and is cost effective.

The session focused on critical aspects for different stakeholders, who shared their views and proposed solutions for increased alignment across stakeholders on an optimal design of master protocols. In particular, it explored whether master protocol designs increased efficiency in drug development in early, late or all phases of development; how far evidence generated from master protocols has been acceptable for key decision making on what molecules to advance to later phases, or informed key regulatory decisions; how far experience of master protocols has confirmed the opportunities and efficiencies they bring to drug development; whether treatment effects of interest are clear in master protocols and multiplicity aspects are sufficiently addressed; concerns relating to statistical methodology; using flexibility of master protocols to add or remove arms in a confirmatory setting; opportunities to further innovate master protocol designs to include adaptive and/or seamless aspects, and/or use external control arms; and the potential for more industry multi-sponsor master protocols, more academic multi-sponsor master protocols, faster review of master protocols by EU regulators, and increased alignment on trial design across regulatory agencies.

Key outcomes on design of master protocols

- *Importance of an early patient engagement*
- *Health Authorities welcome the use of fit- for-purpose master protocols*
- *Need to clearly formulate at an early stage the objective of the trial, the endpoints and key design aspects*
- *More experience is needed in early stages. In later stages we need to ensure we identify the right opportunities, to apply the right available methods (including finding trade-offs) and to discuss key design challenges with regulators and HTAbs early*
- *Need to ensure appropriate sharing of data (during the CT and beyond)*

- *We need to learn from the existing trials and from each other: as an example, Covid-19 platform trials have shown that different stakeholders, academics and regulators can align to design master protocols*
- *Opportunities to expand its use in rare disease and paediatric trials*

Potential solutions/call for action on design of master protocols

- *Need to explore the use of master protocols in confirmatory settings as multi-sponsored studies*
- *Need to increase alignment on trial design across regulatory agencies and HTAbs*
- *Need to develop efficient knowledge sharing platforms between all the key players (academics, sponsors, regulators, HTAbs) to share the learnings and discuss how to advance the field*
- *Separate general clinical trial challenges from the challenges specific to master protocols to advance the field*
- *Need to manage clear accountability by careful agreement upfront*
- *Ensure patients are part of the whole process and are involved early*

Breakout session 2 - Regulatory Processes and System

As the EU regulatory landscape and policy initiatives continue to evolve, this session provided a platform for drug developers, regulators and other stakeholders to discuss the current regulatory process and system for CCT advice and authorisation. It used case studies and research on CCT proposals accepted by regulators to highlight learnings and opportunities for regulatory convergence. A concluding panel discussion provided a perspective on policy opportunities from participants.

The discussion explored unmet need and challenges in drug development for heterogeneous disease and in the face of development difficulty. It considered a study on a Phase 2b Bayesian adaptive randomized clinical trial with response adaptive randomization, the NEOS complex innovative trial design in paediatric multiple sclerosis, a pilot study of personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck, and a comparison of industry experience with a study design both in the US FDA CID Pilot Program and in the EU. Questions examined included whether there is a sufficiently agile and comprehensive platform to support a CCT pilot program in the EU, and what its ideal configuration would be; the potential benefits to different stakeholders of an integrated platform; how soon sponsors should initiate engagement with regulators during the development program; and how HTAbs might be included in an EU CCT pilot programme.

Key outcomes on regulatory processes and system

- *Need in the EU for a process and system for all to share information on CCTs and learn*
- *Several learnings from FDA CID pilot program, program including the benefits from shared learning of all stakeholders*
- *Currently there is no EU platform adequately agile and comprehensive to support a CCT pilot program but there is commitment to explore options and establish it e.g., this could be restricted to selected therapeutic areas*
- *Possible options: INNO project platform, EMA's Innovation Taskforce (ITF), link SAWP/PDCO with EU-IN (MNSA), build on experiences from the EMA-EUnetHTA dialogue*
- *Possibility to enhance collaboration dialogue between EMA and FDA on CCTs*
- *Experience and training need for the system and assessors*
- *Consider the needs of different stakeholders, including HTAbs and payers, when advising or accepting CCTs*
- *Involving patients is critical since they also need to understand the pros and cons*
- *Q&A on relevant questions is being developed by regulatory authorities. HTAbs may also publish guidance in future.*

Recommendations on regulatory processes and system
What should be considered for a possible CCT program in the EU?

- ***Resources and a plan to implement processes and systems to support a CCT*** *pilot in the EU*
- *A unified, interactive, collaborative environment between sponsors and EMA, including:*
  - *Appropriate level of multidisciplinary subject matter expertise and overall experience*
  - *Early dialogue between sponsors and regulatory authorities*
  - *Appropriate frequency of interactions between sponsor and EMA, preferably face-to-face*
- *A sharing of industry and regulator perspective/experience for the broader scientific community*
- *Agreement between sponsors and regulators on complex and innovative trial designs should result in improved efficiency in drug development (and ultimately bringing new therapies to patients who need them)*

Breakout session 3 - Patient Involvement

Patient involvement in clinical trials is attracting increased interest, and experience is growing. This session provided an opportunity to share experience to date and to identify recommendations for optimising patients' involvement in the design and conduct of complex clinical trials.

Presentations from stakeholders included a scene-setting from a regulatory standpoint, with a focus on the implementation of the clinical trial regulation in February 2022; the importance of CCT for paediatric development and of patient involvement in research; the current and potential future role and impact of Public Private Partnership projects from both an IMI and a European Commission representative; and the experience of an onco-paediatrician in conducting trials and interacting with children and their carers. It was stressed that involving patients requires expertise, planning and assessment, and taking account of inclusion, and the process can help sponsors in aspects ranging from defining the most appropriate trial design to addressing the research question or to helping with participants' recruitment.

A review of participants' experience in involving patients in the design of CCTs identified elements to consider to involve 'fit-for-purpose' patients, documenting patient involvement in the CT application, how to use the law at the best to optimize patient involvement in drug development, and possible next steps, including synergies with education and training.

Key outcomes on patient involvement

Paradigm shift: from a drug centric approach towards a more patient-centric approach

Terminology: when determining the appropriate body(ies), Member States should ensure the involvement of laypersons, in particular patients or patients' organisations – CT Regulation Preamble

- *Clear differentiation between lay persons & patient advocates - every caregiver is a 'specialist*

Ensure early and meaningful patients' involvement since this is the best approach to guarantee CT designs are patient-centric

- *Patient engagement is crucial in all trials, including in CCTs*
- *Complexity relates not only to the trials, but also to elements such as rare disease, divergences among health authorities…*
- *Involvement of patient organizations in CT is different across Member States - language barrier*
- *Need for true patient involvement and collaboration – not just a tick-the-box exercise*

Involving patients in CT requires planning and expertise, and therefore a more systematic approach

- *Patients' organisations and established networks, e.g., YPAGs can help sponsors in involving patients in CTs*

IMI and EU funded projects are key and have shown their value

- *Need to secure sustainability and output implementation better*

UK MHRA is also promoting patient involvement in CT development, and has a dedicated team

- *work very closely with the UK Ethics Committees, i.e., through combined reviews of CTs in the UK (Ethics and MHRA) which will become the norm in Jan. 2022.*
- *ILAP (Innovative Licensing and Access Pathway) is a new scheme recently launched which has specific tool for focussing on patient involvement.*

Potential solutions/call for action on patient involvement

Is there a need/value to document patient involvement in the CT application?

- *Regulation (EU) No 536/2014 Annex I (Clinical Trials Regulation) states that patient involvement shall be included in the protocol:*
  "The protocol shall at least include: …(e) where patients were involved in the design of the clinical trial, a description of their involvement)"
- *Develop a section in the CTA which denotes at the co-design stage the perspective from the patient/participant/carer and provide details on how their input made a difference to the design*
- *Still an open question, which would need further discussion*

Ensure early and meaningful involvement of the patients in CT design

- *Companies to ensure that the CT teams value patients' involvement and feedback*
- *How to consider/aggregate the feedback from multiple countries?*
- *Is there a need for contractual framework to ensure proper remuneration, but also confidentiality?*
- *How to measure its impact and make it visible? There is a risk not to involve patient*

Optimise the use of the Patient Engagement Toolbox developed by IMI Paradigm

Need to work towards the capacity building of the patient community; they need good background and expertise on CCT

Training for patients and patient advocates, but also for other stakeholders, e.g., physicians, regulators

Breakout session 4 - Historical Controls and Adaptative Features

This session highlighted two case studies of complex innovative clinical trials that incorporated control data or had adaptive features. The NEOS combined study design for ofatumumab and siponimod illustrated the borrowing of information from external data sources in a randomised paediatric trial in multiple sclerosis. The second used a complex Bayesian adaptive design to explore dose ranging and to generate safety and efficacy evidence.

The discussion shared different stakeholder experiences and views on how to promote the use of such designs, with questions about whether efficiency in drug development has been increased in early, late or all phases of development through incorporating historical information or incorporating other adaptive features or using Bayesian approaches, and whether evidence thus generated has been acceptable for selecting molecules to advance to later phases, or regulatory or access decisions. It also explored stakeholders' views on the acceptability of evidence generated from designs incorporating historical information or response adaptive randomization designs. Design challenges discussed included preferences on sources of historical information (e.g. historical clinical trials or real-world data), management of Type I error, how to ensure that data sources balance quality and relevance, and statistical methodology challenges. Ideas were exchanged on how Europe could establish a collaborative CCT program, and on the future prospects for trials incorporating historical information or with adaptive features including Bayesian methods.

Key outcomes on trials incorporating historical controls or with adaptive features

- *Agencies are open for discussion for new designs, including incorporation of historical data (or RWD) BUT much discussion about management of Type I error and its meaning in the Bayesian context*
- *Sources of data need to be assessed in view of the question at the centre of the trial*
- *Good practice: look at the question first, then look at the available sources of data and last define the global design and approach*
- *Need to draw the line between advice, collaborative discussion between regulators and sponsors and approval activities ("there is no pre-approval")*

Potential solutions/call for action on trials incorporating historical controls or with adaptive features

- *Interest for learning together from both sides*
- *Opportunity for a platform to share experiences, maybe not only on a product basis*
- *Value good practice: have the question first, and then have a multistakeholder discussion in order to better address the question. Explain clearly why you are proposing a given approach rather than the "traditional" approach (e.g., RCT...)*

- *Ensuring data sharing to avoid unnecessary burden, to improve education, training and re-use of data*
- *Need to improve drug development using innovation, not only in paediatrics or rare disease area*

Breakout session 5 - Implementation and Operational Aspects

Complex innovative trial designs require significant upfront planning, anticipation, strong communication and flexible problem-solving approaches across multiple stakeholders. This session discussed each of the steps: planning, implementation, execution and oversight of complex clinical trials to identify the most important challenges. Aspects such as collaboration versus competition, the use of common templates and governance were discussed, drawing on examples such as EU-PEARL, STAMPEDE and RECOVERY, to prompt suggestions of best practices and recommendations.

Discussion covered the intrinsic complexity of these trials and its implications for operational complexity and inter-/multi-stakeholder relationships: while some challenges are specific for CCTs and/or the operational approach, others are merely exacerbations of known issues due to the sheer complexity and scale.

Specific identified challenges concerning trial planning included study design (single vs master + sub-protocols) and adaptations, regulatory availability of scientific advice, whether to choose a collaborative, competitive or mixed operational approach and whether sponsorship or funding is commercial, non-commercial or mixed. Other factors included patient involvement, design, study materials, site selection and investigator involvement, selection of service providers and establishment of oversight bodies, and personnel resources in terms of numbers and training. Challenges identified during trial conduct included data management issues, new safety issues, and applying substantial modifications, such as adding or closing arms/comparisons, or adapting the control arm or the standard of care. In trial reporting, the main challenges identified were timing of the communications and communication of arm-specific vs overall results. The importance was emphasised of careful planning, initially, and with each substantial modification. This implies an early start, in full awareness of the challenges and resource needs, early interaction with regulators and ethics committees, and involvement of all stakeholders.

Key outcomes

Some of the identified challenges are specific to CCTs and/or the operational approach, while others are just exacerbations of known issues due to the sheer complexity and scale.

Trial planning

- *Careful planning is key to success*
- *Very important initially, but also with each substantial modification*
- *The possible operational approaches (collaborative, competitive or mixed) have all pros and cons*
- *Need to start early, and involve all stakeholders*
- *Interact early with patients, regulators and ethics committees*
- *Pay attention to details in the contracts, esp. for multi-sponsor CCTs*
- *Each stakeholder should be fully aware of his responsibilities*
- *Don't underestimate the resource needs, and foresee flexibility and scalability*

- *Templates for several study documents would be welcome*

Trial conduct

- *Start small and scale up as needed. You're in for a long ride*
- *Need to pay increased attention to:*
    - *Trial management issues, esp. concerning substantial modifications, e.g. adding or closing an arm, adapting the control arm or the standard of care, coping with new safety issues*
    - *Data management issues, e.g. CRF and data base updates, data base growth management*
    - *Staff issues, e.g. regular re-estimation of needs, priority setting of competing and concurrent tasks, assurance of continuity, increased attention to workload, stress and motivation*
    - *Regular communication between all stakeholders, esp. in CCTs initiated by a consortium*

Trial reporting

- *CCT-specific challenges: timing of the communications, arm-specific vs overall results*
- *Need for more specific regulatory guidelines: foresee more modularity and flexibility, and leave some choice to participants*

Trial oversight (Trial Management Group, (i)Steering Committee, (i)DMC)
Special attention required to manage:

- *Multiple arms/comparisons > install arm-specific expert subgroups*
- *Long trials > assure continuity of membership*
- *Independency, esp. for industry-sponsored CCTs > independent DMC for all CCTs?*

Potential solutions/Call for action

1. *In order for CCTs to be successful, the operational approach chosen for their planning, conduct and reporting, i.e. competitive or collaborative, should be fit-for-purpose.*
2. *There is an urgent need to create a common forum for CCTs in Europe, where all stakeholders can share operational experiences and best practices, in strong public-private partnership.*
   In this respect, the EU-PEARL initiative seems to show the way forward, in creating Integrated Research Platforms and study document template, initially for 4 therapeutic areas in big medical need for innovation (MDD, TB, NASH, NF), but also useful in other areas in the future.
   Therefore, should and could EU-PEARL be extended or mirrored in some form?

Breakout session 6 - Education and Training

A healthy clinical research environment requires sufficiently familiarity with complex innovative clinical trials among patients, regulators and HTA bodies, ethics committees, investigators and sponsors. This session provided an update on available education and training material, and identified training gaps regarding CCTs. The session helped to assess the most pressing educational needs for the various stakeholders, and brainstormed on the most appropriate organisations to provide such training and to develop the necessary material and guidance.

Discussion ranged across participants' views on where is there a need for more targeted education, whether it was adequate for patients, investigators, sponsors, and what is still needed, or the difficulties of finding appropriate training. It revealed wide gaps between supply and demand, but examples of successful initiatives were included. What metrics could be used to evaluate the usefulness of particular training initiatives, how training helped during specific tasks, and whether it was fit for purpose were also explored.

From the patient perspective, the European Patient's Academy (EUPATI) or EURORDIS Open Academy are considered good sources for basic information, but resources are insufficient for complex clinical trials, and when specialised knowledge is required, expert training may be required, which is beyond the budget of patient advocates and patient organisations. The problem is all the more acute for less experienced patient advocates working only at national level.

Some regulators receive in-house trainings or attend conferences or workshops, but in most health authorities structured training is not yet available, and experience is gained through learning by doing. Ethics committees, with their diverse membership, face serious challenges, and currently little specific training is available – although the UK health authorities organised a series of regional ethics committee workshops. Some HTAbs interact with regulators on CCTs, but with distinct assessment focuses and little alignment. Some governments have committed to programs to embed expert understanding on innovative trials, which could benefit investigators and clinical staff. Among sponsors, internal development of training on complex clinical trials remains ad hoc and uncoordinated, with training often trial-specific and not easily replicable, and the potential of public private partnerships has not yet yielded wide-scale education and training for CCTs.

Discussion covered the interest in and feasibility of an EU-wide or international initiative, with the suggestion that delivery of education and training material should be part of any initiative by European regulators on CCTs.

Key outcomes on education and training

- *Complexity of trial is increasing and the need for training is higher*

- *Useful material is already available but limited to closed communities. Experience sharing and common templates will help to streamline and optimize the implementation and operations of complex clinical trials*
  - *Whose responsibility is it to organise, update and share the learnings/trainings across all key players?*
- *Take time to build a 'centre of excellence' to establish the necessary connections between all the stakeholders*
- *Importance of the involvement of patient experts at each step and at each level, especially at a national level*
- *Need to lower barriers of education, and find a solution to subsidise funding of patient training*

Potential solutions/call for action on education and training

- *Need to develop efficient knowledge sharing platforms (e.g., peer coaching, discussion groups) between all the key players to share learnings*
- *Need to develop trainings with all key players accessible to everyone (e.g. without languages, geographical or financial barriers)*
- *Need modular training for CCTs (especially for RECs), addressing general aspects, as well as targeted training for specific subgroups*
- *Need to include trainings in the curriculum of medical staff and ensure access to the appropriate courses*

Annex 3

Questions & Answers (Q&A)

Question	Reply
The iterative process used by FDA in their CID pilot in order to clarify the trial design seems important. Would CTFG support a pilot for such an iterative advice approach to CCT in EU?	The major difference between US and EU is the fact that in the EU, marketing authorisation and CT authorisation are separate. So it would not only be CTFG but also EMA to avoid issues with acceptability of data
Could it also be considered to describe the involvement of investigator sites in the protocol? - to make it more clear to regulators/EC that sponsor has considered and optimized the facilitation of the operational setup at the study site	Would this jeopardize the independence of the Investigators?
So the fact that EMA does not initially agree with the initial design of a trial does not mean that if efficacy is demonstrated it can be submitted and approved for that indication?	The SAWP works on behalf of the CHMP and we never do pre-assessment. We can express that we think a trial design is not suited and we think it will not generate interpretable data in worst case but that is not legally binding.
	And not every drug development comes for SA, so some drugs come to the submission with plans that have never been discussed with regulators
In oncology, biomarker enriched trials are more and more common. With IVDR coming into place and impacting the requirements for CDx used to enrich trials, is CTFG / CTEG / EMA working on clarifying guidance or Q&As?	I think there will come something, once we understand the regulation ourselves and COVID is over.....
How can we help to advance the discussions together between industry, regulators and HTA bodies?	Great idea! Maybe would be meaningful to include patient organizations in these discussions?
What does Type 1 error mean anyway in a fully Bayesian design? Shall we move beyond p-values…	Or stick with p-values and not go Bayesian?
What is the difference between a platform trial as compared to a umbrella/basket trial?	A platform trial is a perpetual umbrella trial.
	So it is just an open-ended umbrella trial?
Within the frame of EU Regulation n°536/2014, will CCTs be managed through CTIS?	Yes

Annex 4

Workshop agenda

Day 1 – 5 October 2021

13:45	**Connection to virtual room and technical checks**	
14:00	**Welcome & Introduction**	**Sini Eskola (EFPIA) & Jan Geissler (Patvocates)**
14:10	**Session 1 – Setting the scene & Sharing experience – CTA approval**	**Anja Schiel (EMA SAWP, NoMA)**
5'	• Introduction	Anja Schiel (EMA SAWP, NoMA)
15'	• CTFG experience of CCTs	Elke Stahl (CTFG, BfArM)
15'	• US pilot feedback - FDA's experience so far	Dionne Price (FDA)
15'	• CTTI, European initiatives, IMI EU Pearl	Solange Corriol-Rohou (AstraZeneca, EFPIA)
15:00	**Session 2 - Stakeholders' priorities & expectations**	**Claas Röhl (NF Patients United)**
10'	• Patients	Dominique Hamerlijnck (EUPATI)
10'	• Regulators - EU & beyond	Anthony Humphreys (EMA)
10'	• Ethics Committees	Martin Brunner (Ethics Committee, AT)
10'	• HTA bodies	Niklas Hedberg (TLV SE, EUnetHTA)
10'	• Sponsors: Industry, Academia & non-profit organisations	Lucia D'Apote (Amgen, EFPIA)
10'	• Investigators	Birgit Geoerger (Gustave Roussy Institute, FR)
25'	• Panel discussion	
16:25	**Coffee break**	
16:45	**Breakout sessions**	
	• Design of Master Protocols	Chairs: Christine Fletcher (GSK, EFPIA) & Lada Leyens (Roche, EFPIA)
	• Regulatory processes and system	Chairs: Anja Schiel (EMA SAWP, NoMA) & Lucia D'Apote (Amgen, EFPIA)
	• Patient involvement	Chairs: Claas Röhl (NF Patients United, AT) & Solange Corriol-Rohou (AZ, EFPIA)
18:45	**Concluding remarks**	**Christine Fletcher (GSK, EFPIA), Mireille Muller (Novartis, EFPIA) & Anja Schiel (EMA SAWP, NoMA)**
19:00	**End of Day 1**	

Day 2 – 6 October 2021

13:45	**Connection to virtual room and technical checks**	
14:00	**Introduction to Day 2**	**Sini Eskola (EFPIA) & Peter Arlett (EMA)**
14:10	**Session 1 – Feedback from Day 1 Breakout sessions**	**Breakout sessions Chairs**
14:40	**Session 2 – Breakout sessions**	
	• Trials incorporating historical controls or with adaptative features	Chairs: Christine Fletcher (GSK, EFPIA) & Frank Bretz (Novartis, EFPIA)
	• CCT implementation/operational aspects	Chairs: Olga Kholmanskikh (CTFG, FAMHP) & Josse R. Thomas (Ethics Committee, BE)
	• Education & Training	Chairs: Begonya Nafria Escalera (eYPAGnet, ES) & Mireille Muller (Novartis, EFPIA)
16:40	**Coffee break**	
16:50	**Feedback from Day 2 Breakout sessions**	**Breakout sessions Chairs**
17:20	**Panel session to discuss main outputs & propose next steps/action plan**	**Moderators: Anja Schiel (EMA SAWP, NoMA) & Nick Sykes (Pfizer, EFPIA)**
	• EU Commission	Kristof Bonnarens (EC DG SANTE)
	• FDA	Dionne Price (FDA)
	• CTFG	Elke Stahl (CTFG Co-Chair, BfArM)
	• Ethics Committees	Josse R. Thomas (Ethics Committee, BE)
	• Patient representatives	Rita Magenheim (GENTURIS)
	• HTA bodies	Niklas Hedberg (SE TUV, EunetHTA)
	• Industry	Christine Fletcher (GSK, EFPIA)
	• NGO	Stephane Lejeune (EORTC)
18:20	**Concluding remarks**	**Christine Fletcher (GSK, EFPIA), Mireille Muller (Novartis, EFPIA) & Anja Schiel (EMA SAWP, NoMA)**
18:30	**End of Day 2**	

Annex 5

List of speakers

List of speakers

Alexandru Costescu	European Commission
Anja Schiel	Chair EMA SAWP, NoMA, Norway
Ann Marie Janson Lang	CTFG Co-Chair, MPA Sweden
Antony Humphreys	Head Regulatory Science Strategy Task Force, EMA
Begonya Nafria Escalera	eYPAGnet, Spain
Birgit Geoerger	Gustave Roussy Institute– France
Cecile Spiertz	EU-PEARL consortium - Janssen
Christine Fletcher	GSK -EFPIA
Claas Röhl	NF Patients United, Austria
Dieter Haering	Novartis
Dimitrios Athanasiou	EURORDIS Board Member in World Duchenne Organization, European Patients Forum
Dionne Price	Director, Division of Biometrics IV, CDER, FDA
Dominique Hamerlijnck	EUPATI
Elke Stahl	CTFG Co-Chair – BfArM; Germany
Frank Bretz	Novartis - EFPIA
Hans Joachim Helms	Roche
Heinz Schmidli	Novartis
Jacoline Bouvy	Technical Director, NICE Scientific Advice
Jan Geissler	Patvocates
Josse R. Thomas	BAREC, Belgium
Juliana Sholter	Amgen
Kristof Bonnarens	European Commission, DG SANTE
Lada Leyens	Roche - EFPIA
Laurence O'Dwyer	Chair EU-IN - HMA, HPRA
Lucia D'Apote	Amgen - EFPIA
Marius Thomas	Novartis
Martin Brunner	Ethics Committee, AT
Matthew Sydes	Professor of Clinical Trials and Methodology, MRC Clinical Trials Unit, UCL
May Mo	Amgen
Mireille Muller	Novartis - EFPIA
Nathalie Seigneuret	IMI
Nick Sykes	Pfizer-EFPIA
Niklas Hedberg	SE TUV, EUnetHTA
Olga Kholmanskikh	CTFG – FAMHP, Belgium
Peter Arlett	Head of Data Analytics and Methods Task Force, EMA
Rita Magenheim	ePAG- GENTURIS
Ruchi Upmanyu	Roche
Sandra Petraglia	CTFG, AIFA Italy
Sharon Love	UCL
Sini Eskola	EFPIA secretariat
Solange Corriol-Rohou	AstraZeneca - EFPIA
Stephane Lejeune	EORTC
Stéphanie Kromar	EORTC