Innovative monitoring technology in clinical trials: feasible approaches, valuable evidence

RSNN session @ FIGON-DMD 2019 – Key Takeaways

On the 23rd of September 2019 the RSNN hosted a session during the FIGON Dutch Medicines Days (www.figondmd.nl) in Leiden. The session was chaired by Peter van Meer (assessor at CBG-MEB, vice-chair RSNN) and Joop van Gerven (chair of the CCMO).

In four presentations, followed by a plenary discussion, current developments in monitoring and measurement technologies for clinical research were discussed. Furthermore, speakers debated on opportunities for optimizing the value of innovative technologies for medicines development and regulatory decision-making. Ultimately, the discussion explored the implications for regulatory and HTA assessment with a special focus on the acceptability of new methods for evidence generation.

Speakers

Matthijs Kruizinga, Research Physician (Juliana Kinderziekenhuis; CHDR)
Tom Zwart, PhD Candidate (Dept. of Clinical Pharmacy and Toxicology - LUMC)
Peter Mol, Principal Assessor (CBG-MEB)
Lourens Bloem, PhD Candidate (Division of Pharmacoepidemiology & Clinical Pharmacology – UU), Pharmacovigilance Assessor (CBG-MEB)

INNOVATIVE MONITORING AND MEASUREMENT TECHNOLOGIES IN CLINICAL RESEARCH

Telemedicine

In the era of digital innovation, patient monitoring has seen rapid and multi-faceted advancements. Not only is telemedicine a powerful tool to continuously measure the status and progression of certain symptoms of a disease in a home environment (applicable to a wide range of diseases), it also gives opportunities to measure disease parameters and test new medication in specific patient populations. This applies in particular to children and the elderly, where trials in a hospital setting are not always practically feasible or reliable. Remote monitoring can overcome logistical challenges (e.g. hospital visits during a busy school schedule or incapability of elderly to reach the hospital) and replace some of the current more invasive monitoring methods. However, acceptance of these new methods for regulatory and HTA decision-making requires that new digital endpoints are validated. Moreover, researchers, physicians, patients and caretakers must be trained to implement remote monitoring technology in their daily life and work routines.

Matthijs Huizinga conducts a series of paediatric clinical trials at the Juliana Children Hospital in which home monitoring is used to measure relevant parameters for chronic and acute paediatric diseases. The tools used for these studies are digital questionnaires (apps) and wearable devices that measure disease specific parameters. Surprisingly, children have no difficulties with these novel technologies because compliance is remarkably high (>90%). An overall challenge with new digital technologies is the selection of parameters to measure. As Dr Huizinga remarks “We always try to make an informed decision on the digital measures to choose for the first set of trials. It may turn out to be the wrong measures and we have to start all over.”
With regards to the validation of new digital endpoints, the priority is the analytical and clinical validation of the new tools in patients and healthy subjects in order to answer questions about reliability of digital measurements and tolerability when devices are used by children. Other unknowns to be tested are the ability of the measurement to detect changes in parameters between healthy and ill children and a correlation with existing measures of disease activity. The final step in the validation process is to test whether a device can detect the effect of a medical intervention on candidate endpoints.

Microsampling

A different application for home-based drug monitoring is microsampling, currently tested at the LUMC in Leiden by comparing conventional venepuncture sampling at the clinic by ‘dried blood spot’ (DBS) sampling at home. Tom Zwart, who is conducting the research,

explains the pros and cons of this type of microsampling for therapeutic drug monitoring and drug testing. As with digital devices, home-based sampling has many potential advantages for patients and shows several opportunities for clinical research. However, besides technical and logistical challenges that need to be overcome (e.g. assay sensitivity, analyte stability, bioanalysis and sampling errors), the implementation of this new tool in clinical trials needs extensive preparation, i.e. guidance and training of patients and clinical staff. In addition, validation of endpoints and acceptance for clinical use is becoming more complex because of the frequent technological improvements. Although innovations in this field make the procedure more reliable and easier to use, it creates new regulatory challenges that need to be addressed appropriately. With wearable blood sampling devices in the pipeline for future 'at-home sampling' methods, early interactions with and between regulatory bodies and notified bodies - also to clarify their respective roles - are essential to ensure successful implementation in medicine development.

ACCEPTABILITY OF NEW METHODS: EVIDENCE BUILDING FOR REGULATORY AND HTA DECISION-MAKING

Closing the knowledge gap between existing and new technologies

For both digital and non-digital home-based monitoring technologies used for drug testing, an early regulatory interaction is required in the setup and execution of clinical trials in order to provide guidance on policies and requirements. Important aspects to take into consideration are a clear definition of clinical endpoints, the context of use, the clinical value and the clinical usability and acceptability of new technologies, as well as the status of similar technologies in European registries. Furthermore, a full understanding of the technical aspects of novel remote monitoring tools, including wearable devices, are of particular importance for qualification and approval. For example, if the clinical evidence (e.g. response to treatment) is based on algorithms, to which extent is the regulator expected to understand the details of such algorithm and how should these algorithms be evaluated? A clear answer to this cannot be given yet, however, in the near future it is expected that regulatory agencies, notified bodies and HTA bodies need to strengthen their teams with experts in this field to make better informed decisions. Peter Mol (principal assessor at CBG-MEB and member of EMA's Scientific Advice Working Party) concluded that devices for remote monitoring bring in an entire new complexity to judging drug efficacy and therefore it is important to close the knowledge gap between existing and new technologies.

Improve evidence building and take away barriers for approval

Another important prerequisite to enable effective use of such new technologies in drug development is timely discussion with and among the different stakeholders involved in the drug life cycle (e.g. regulators, HTA agencies, physicians, patients), as discussed in the presentation of Lourens Bloem. It was pointed out that remote monitoring technologies can also be applied to support the accelerated or conditional approval of new medicines, especially in areas of high unmet medical need. At the same time, innovative evidence generation technologies potentially lead to more uncertainty, due to lack of (specific) expertise, lack of experience or, possibly, lack of trust, which may create barriers for innovative drug development and ultimately patient access to these drugs. Therefore, early multi-stakeholder discussions are required to facilitate medicine developers and authorities to proactively manage these uncertainties.

THE WAY FORWARD

During the discussion it was highlighted that the CE-marking of a device for technical validation, will help in the decision-making, but is officially not a prerequisite for validation of a product. For a qualification advice or opinion, on the other hand, CE-marking can be supportive for a positive outcome. Nevertheless, it should be noted that regulatory policies on CE-marking can be substantially country-specific. Alignment on regulatory decisions within (European) countries would take away uncertainties, particularly in multi-country clinical trials.

Another barrier that needs to be overcome is the alignment with HTA bodies. In a typical regulatory process, regulators (assessing benefits/risks of a new product) and HTA bodies (assessing relative cost-effectiveness) require different data sets to build their case for approval. It is currently being assessed by a pilot from the Medicines Evaluation Board (MEB), if the provision of the same data for both types of qualification would benefit the overall approval procedure. Eventually, innovative monitoring technology can be used in clinical trials to collect longitudinal clinical data (e.g. quality of life data) to bridge the evidence gap between regulators and HTA, and support HTA decision making.

Finally, evidence building for technologies that measure on a continuous scale and potentially produce a wide range of data is challenging. Providing subjective patient data such as ‘quality of life’ measurements can be of value. These data might seem irrelevant for qualification but can support the clinical value of a new tool, especially if it concerns non-invasive methods that can replace invasive measurements. In the end, the philosophy behind regulation of new technologies is not different from the regulation of standard medicinal products: a drug or device should be sufficiently efficacious without causing unacceptable harm to the patient. Therefore, regulators call for an open discussion about

new tools and technologies for clinical use and medicine testing in order to better understand all aspects necessary for qualification and validation. Early recommendations by regulatory agencies and HTA bodies, and interactions with physicians and patients via the EMAs Scientific Advisory Groups, can help in establishing an acceptable uncertainty threshold and ensuring timely patient access to innovative treatments and use of new technologies. In this context it is important that the implementation of new methods is supported in such a way that the right balance is struck between validating a new method by comparing them to previous standards (e.g. HAM-D scales in major depressive disorder) without creating barriers that stymie innovation.

In conclusion, key areas for future research that emerged from the session are:

- Assessment of the benefit of early interactions:
    - between the developers of medicines and monitoring technologies with regulatory authorities at the design stage of new clinical trials.
    - between different agencies at the EU and national level (regulators, notified bodies, HTA agencies), and any (future) regulators focused on the use of algorithms, big data analysis methods and advanced technologies.
- The observed mismatch between technology push (e.g. wearables, remote monitoring, mHealth) and regulatory pull (e.g. regulatory acceptability) needs fostering research into critical obstacles and barriers.
- The conceptualisation and role of uncertainty in decision-making relating to the use of innovative monitoring technologies.

The results of this session will be addressed by the RSNN in future research agenda's in order to support further decision-making.