BEST PRACTICES FOR USE-RELATED RISK ANALYSIS THROUGH COLLABORATION OF HUMAN FACTORS AND CLINICAL

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Integrating the Human Factors Engineering (HFE) process, and its user-centered approach, into the medical device and combination Product Development Process (PDP), has been an ongoing challenge for its respective industries and Human Factors (HF) practitioners within it for decades. Yet, despite continuous process adaptation and evolution of the HFE process, as well as the introduction of standards and health authority guidelines, the early integration of a risk-based and user-centered approach within the development and design process remains an ongoing practical challenge occupying the minds of most. With the introduction of the European MDR 2017/745 in 2017, an additional emphasis was put on the importance of use-related risk identification, assessment, and data based evaluation within the clinical evaluation process, and with such introduces clinical teams to (new) 'use-related risk challenges' as well.

This paper provides a framework for early integration of an iterative use-related risk analysis approach, addressing common practical challenges, and providing best practices for such. Furthermore, it highlights how applying a collaborative approach between HF and clinical efforts would permit for collection of more robust use-related data sets, thus potentially optimizing use-related risk, residual risk, and risk-benefit analyses and their processes.

Introduction

Integrating Human Factors (HF) and its user-centered approach and corresponding Human Factors Engineering (HFE) process, into the medical device, and pharmaceutical combination Product Development Process (PDP), has been an ongoing challenge for its respective industries and HF practitioners within it for decades.

For medical device, and pharmaceutical combination products this journey of integration started in the 80s when the U.S. Food and Drug Administration (FDA) proposed a risk management approach to its respective industry product development processes (FDA 2000; FDA 2016a; FDA 2016b; Israelski & Muto 2011). Key importance of an early integration of a combined risk-based and user-centered design approach was subsequently identified in FDA's 2000 guidance "Incorporating Human Factors Engineering into Risk Management". Within such, the authors Kaye and Crowley stressed that "*rare or unusual use scenarios resulting in hazards with serious consequences often prove to be the greatest threat to safe and effective medical device use after a device becomes available for general use,*" as "*users are often not prepared for infrequent, unexpected use scenarios because they are often not dealt with adequately in device design, training, or operating instructions,*" and with such highlighted that while "*infrequent but dangerous use scenarios are often difficult to identify,*" it "***underscores the necessity for careful application of the analytic and empirical approaches early in, and throughout the design process.***"

And while HF as a scientific discipline remains constant in its principles and foundation; technology, tools, and materials, as well as PDP approaches, e.g., waterfall model, agile developments, and digital healthcare, as well as various other factors have evolved and directly impacted the demands and expectations of and on the HFE process. Intensifying the challenge of a combined risk-based and user-centered design approach is the evolution of healthcare itself, as such has introduced new types of medical devices with the widespread adoption of computerization, further adding yet another layer of complexity to an already complex environment (Easty 2018). Easty further explains that often these newly complex systems and devices are introduced in ways that fail to take into account the environment of care, and/ or the skills, abilities, and training of the users, leading to new possibilities for (use-related) error (Easty 2018).

At the 2022 Healthcare Systems Ergonomics and Patient Safety (HEPS) conference, the "EU HF forum" reiterated these ongoing challenges in a special session for 'use-related risk management for medical devices and combination products.' Here, Stüdeli (2022) presented peer feedback of collected interviews and discussion rounds with human factors engineers (n=15) within the industry, echoing the sentiments in challenges, and identifying current key practical challenges regarding use-related risk management:

- When to perform use-related risks analysis, and in what depth?
- From a sequence of events perspective: what are reasonable hazardous scenarios?
- How to deal with probability numbers for use-related risks?
- How to deal with those hazard-related use scenarios not selected for (summative) evaluation?
- How to define acceptance criteria (for critical and non-critical tasks)?
- When is a use-related risk mitigation achieved? What is a reasonable and/ or practical mitigation?

Mehrzad, H.M., Stüdeli, T. & Quie, H. (2023) Best practices for use-related risk analysis through collaboration of human factors and clinical, In: 12th International Symposium on Human Factors and Ergonomics in Healthcare (HCS 2023), March 26-29, 2023, Orlando (FL). Online: https://www.hcs-2023.org/

- How to deal with residual use-related risks and the risk-benefit analysis?

Thus, recapping, that despite continuous adaptation and evolution in the field, e.g., IEC 62366-1, from its original draft in 2005 to its latest amendments in 2020 (FDA 2020), as well as various publishing around the topic by multiple health authorities (US, UK, China), the early integration of a combined risk-based and user-centered approach within the medical PDP, including implementation and execution of appropriate use-related risk management, remains an ongoing practical challenge occupying the minds of most practitioners.

The impact of continuous adaptation and evolution within the medical device and combination PDP though has not been exclusive to the HFE process. It has also affected the clinical evaluation process and its requirements, as with the progression of human factors and usability (engineering) standards and guidelines, the European Medical Device Directive also underwent an evolution addressing "usability" and its associated risks.

Furthermore, as industry is increasingly learning the nuances and advantages of "real world" over "simulated-use" data, a convergence of HFE and clinical efforts has become unavoidable; and the demand for guidance on how to execute such convergence and collaborate amongst HFE and clinical teams has soared.

While US FDA answered with draft guidances such as "Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development" in 2016 (FDA 2016a), and "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" in 2017 (FDA 2017), the European Medical Device Directive (EU MDD) did as well with the publication of its Medical Device Regulation (MDR) 2017/745, in which it introduced an increased demand on usability requirements within the clinical evaluation process.

While under the original MDD 1993/42/EEC initial usability requirements were addressed, with the issuance of IEC 62366:2007, progression was introduced when first amendments were made and published under MDD 2007/47/EC to further highlight the importance of usability and its associated risks by specifically including essential requirements for manufacturers to address and carefully evaluate risks caused by "non-usable medical devices", i.e., use-related risks.

Then, in 2017, and in response to the 2015 IEC 62366-1:2015 standard, the European MDR 2017/745 directive sought further alignment with usability standards by specifically highlighting risks associated with:

- "ergonomic features of the device",
- "environment in which the device is intended to be used", and
- "technical knowledge, experience [...] and training, and where applicable, the medical and physical conditions of intended users"

One of the European Commission's purposes for the MDR was to ensure transparency and data sharing between teams during product development, with the goal of further increasing patient safety. Accordingly, and with the same goal of increasing patient safety, language changes within the MDR now require manufacturers of lower risk class products to provide clinical evidence directly from the patients and/ or users, where previously they might have been able to provide such via literature review, thus creating a greater burden on clinical evaluation for such manufacturers.

With this publication and its emphasis on the importance of use-related risk identification, assessment, and data based evaluation of such within the clinical evaluation process, it also introduces clinical teams to new 'use-related risk challenges' as well.

And while MDR 2017/745 usability requirements are evaluated during human factors summative usability studies, such is done predominately without any interaction between human factors and clinical teams; missing out on opportunities to harmonize usability and clinical evaluation efforts and collect more robust data sets, in which usability and clinical evaluation activities take into consideration one another's requirements and goals.

Likewise, clinical risks are evaluated (and mitigated) predominantly with clinical data, with no input from HF teams; despite, residual risk and risk-benefit determination being equally dependent on HFE's use-related data collected during human factors usability studies, addressing the evaluation and validation of risks associated with intended use, user, and use environment. Here again, the lack of interaction between clinical and human factors teams proves a clear disadvantage for both.

In particular, Annex I of MDR 2017/745 requires clinical evaluation to adequately address the qualitative and quantitative aspects of clinical safety with clear reference to the determination of residual risks and undesirable side effects to provide confirmation of the relevant safety and performance requirements provided related to such (MDCG 2020). These safety and performance requirements are intertwined between clinical and usability requirements and activities, and thus naturally lead to the need for usability and clinical specialists to work together to identify and assess remaining residual risk(s).

This intertwining of requirements is again amplified in one of the MDR's key technical documents, the Instructions for Use (IFU), as such provide the essential information to the final user. As the IFU is based on input from clinical evaluation data regarding safety, it also describes residual risks and any undesirable side effects, and includes these identified residual risks based on the analysis of the use-related and clinical risks "Information on any residual risks and any undesirable effects, warnings and precautions (MDR, Article 32. 2, h)."

This again demonstrates the intertwining of usability and clinical, and shows the dependency to one another, which again is also shown under Section G in the MDCG 2020-7 (MDCG 2020), as the clinical evaluation should consider the above points, but also clearly answer use-related questions, such as:

- Is the device to be used by healthcare professionals or lay users?
- Does the IFU provide all the appropriate/relevant information for the intended user?
- Has the manufacturer taken into account the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).
- Is any training for users required as a risk control measure? If not, is this justified with respect to the risk management file and the clinical evaluation?

When looking for a direct link between usability and clinical requirements within the MDR, Annex II describes contents of its technical documentation, which are directly taken from the Human Factors/Usability Engineering (HF/UE) file:

- A definition of the intended users,
- A description of which other devices the device can/should be combined with/connected to, and
- Tests and test results.

This further substantiates that measures to evaluate and validate these (clinical) requirements could be merged into one shared (study) protocol, collecting data for both, clinical and usability requirements.

Evolution however did not stop at pre-market PDP alone. The MDR also stresses the importance of usability input into clinical evaluation within post-market surveillance requirements. It uses and highlights the term "usability" directly under Article 83(3), stating that manufacturers are expected to "gather data" within a "post-market surveillance system", with respect to "the identification of options to improve the usability, performance and safety of the device." Annex III further clarifies and specifically outlines which information must be collected and analyzed with respect to such, e.g., information concerning serious incidents, including information from PSURs, and field safety corrective actions, records referring to non-serious incidents and data on any undesirable side-effects, information, including feedback and complaints, provided by users, distributors, and importers, etc.

Part of the Post-Market Surveillance (PMS) plan is the Post-Market Clinical Follow-up (PMCF) plan. The PMCF requires continuous updating to clinical evaluation, in which the manufacturer shall

- proactively collect and evaluate clinical data with the objective of verifying the safety and effectiveness of the product throughout its expected lifetime,
- identify previously unknown side-effects,
- monitor identified side effects and contraindications, monitoring emerging risks based on factual evidence, ensuring the continued favorable benefit-risk ratio, and
- identify and address any systematic misuse or off-label use, taking appropriate preventive and corrective actions if and when necessary.

Here, the PMCF as well integrates both usability and clinical evaluation together. It's mandating the documentation of specific activities within its framework, one of which entails the identification and description of the general methods and procedures to be implemented in the PMCF, such as the collection of clinical expertise acquired, user feedback, a thorough examination of scientific literature, and an examination of other sources of clinical data.

The comprehensive implementation of these activities results in the availability of data that the manufacturer can utilize for further risk mitigation and future product development. Hence, it is of paramount importance to ensure all required information is collected and analyzed involving risk management, clinical, and HFE experts, during all phases of the PDP, including planning, execution, and analysis stages, to ensure appropriate and robust data. This process should ideally be documented to allow for evaluation of further opportunities, e.g., product usability enhancements, to allow the manufacturer to demonstrate such with examples. Furthermore, the findings of the PMCF should be analyzed by the manufacturer and documented in a PMCF evaluation report, which is incorporated into the clinical evaluation report and technical documentation.

Considering this, a collaborative approach between human factors and clinical teams has become a necessity to ensure compliance with MDR. §33 states (MDR 2017): "The risk management system should be carefully aligned with and reflected in the clinical evaluation for the device, including the clinical risks to be addressed as part of clinical investigations, clinical evaluation and post-market clinical follow up. The risk management and clinical evaluation processes should be inter-dependent and should be regularly updated." In addition, it could allow for potential hybrid data collection activities and studies addressing evaluation of both, clinical and use-related risks, and with such optimize residual and benefit-risk analyses, and subsequently enhance HFE and clinical evaluation processes and reporting. Moreover, it would provide for a more robust data set being available to the manufacturer to use for advanced device development, as well as potential further risk mitigation.

Best practices for early integration of iterative use-related risk analysis into the PDP and successful execution through collaboration of human factors and clinical evaluation

The following framework is based on the regulatory requirements discussed above and addresses the discussed prevailing key practical challenges by pointing out their common pitfalls and offering best practices to mitigate such within each phase of the commonly applied five phases of the medical device development process. Though these best practices may serve to facilitate the integration of a combined risk-based and user-centered approach, and its early and iterative use-related risk analysis development within the medical device development process, each product development process (PDP) is singular, and must be tailored to the specific requirements of the product in question. Thus, not all recommended practices will be applicable to each PDP. Accordingly, HFE activities should always be carefully adapted and scaled to the actual need of the product applicable.

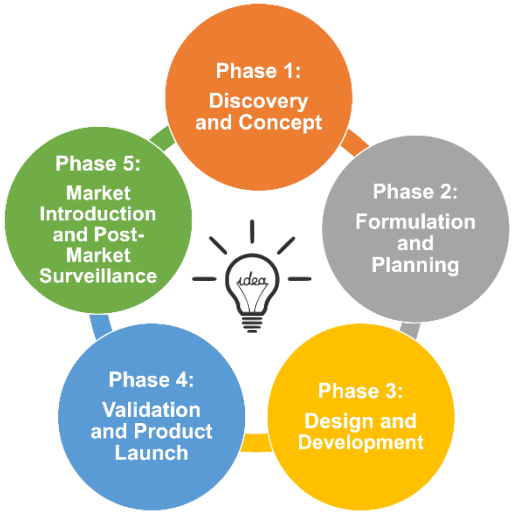

Figure 1: The typical 5 phases of the Product Development Process (PDP) within medical device development.

Phase 1: Discovery and Concept

Pitfalls:

The initial phase of the PDP is often characterized by the absence of a systematic evaluation of risks and a preoccupation with market appeal, business prospects, and user experiences. Discussing hazardous use scenarios and the possibility of use-related issues and potential use problems during this phase is often viewed as a deterrent to innovation.

Good practices:

- Conduct early exploratory research identifying current use-related issues within the field. Ensure data collected in early research includes current and potential hazardous use scenarios with respect to current products on market addressing your intended use concept, e.g., known use problems analysis.
- Use clinical resources, e.g., literature, patient groups etc. for the planning of your observational field research with respect to use-related risk perception and safety aspects.
- Leverage a systematic, task-based analysis approach to identify both potential hazards and/ or hazardous situations, as well as design (and corresponding mitigation) opportunities.

Phase 2: Formulation and Planning

Pitfalls:

It is not uncommon for development teams to operate in isolation, with a primary emphasis on their own tasks and documentation. This tendency results in the formation of discrete silos for each team, e.g., human factors engineering, clinical evaluation, and risk management. This fragmented approach to critical planning documents, such as Human Factors/Usability Engineering (HF/UE), Clinical Evaluation, and Risk Management Plans, lacks coordination and inter-team input, resulting in superficial "checklist" documents that do not contribute substantially to the development process or plans.

Good practices:

- Draft an initial framework of the device task analysis and identify potential use problems, e.g., use errors, close calls, and use difficulties, related to all tasks within.
  Note: *Ensure to identify potential use scenarios that could lead to tasks not being performed and/ or being performed incorrectly by the (intended) user.*
- Ensure to include use-related risks, usability, clinical, and risk management requirements sections in HF/UE, clinical evaluation, and risk management plans, clarifying identification, integration, evaluation (and potential validation) activities within their processes, and how such can supplement and support the other.

Phase 3: Design and Development

Pitfalls:

Occasionally, the device design process prioritizes use(r) preferences, acceptance, and performance above all else during (early) design evaluation, leading to a “tabling” of safety-critical use scenarios and associated potential risks, often determining them as “out of scope.” This tendency is often driven by a perception that addressing use-related issues constitutes a

hindrance to the project and its (timely) progress, rather than an opportunity to enhance the design, improve usability, and proactively mitigate use-related risks.

Good practices:

- Utilize formative human factors usability studies (simulated-use) to assess early prototypes, often and iteratively, to gain insight into their actual use in both positive and negative use scenarios with respect to use(r) preferences, acceptance, performance, as well as potential use-related risks.
- Document any use problems, including use errors, close calls, and difficulties, whether observed and/ or reported, and subject them to a level of analysis equivalent to that performed for use(r) preferences, acceptance, and/ or performance.
- Employ the realism of real-world settings in clinical studies, when feasible and appropriate, to evaluate the efficacy of your early design concepts.

Phase 4: Validation and Product Launch

Pitfalls:

Again, in some instances device design undergoes only partial evaluation in later stages as well, prioritizing use(r) preferences, acceptance, and performance, while safety-critical scenarios fall outside the scope of testing. Here, again., use-related issues are viewed as obstacles to the project's progress, rather than opportunities for improvement.

Furthermore, when the siloed approach persists into verification and validation phases, validation plans are frequently devised in isolation, with limited inter-team collaboration among human factors engineering, clinical evaluation, and risk management teams. This approach precludes the possibility of jointly planning, designing, and conducting activities and studies to evaluate and validate usability, clinical evaluation, and risk mitigation requirements, thus limiting the scope and robustness of generated data, including the capacity to capture more elusive data points, such as those addressing knowledge tasks for example.

Good practices:

- Collaborate between human factors engineering, clinical evaluation, and risk management teams and provide input to another's evaluation and validation plans.
- Align goals of human factors and clinical evaluation studies with respective requirements, e.g., identify opportunities for hybrid data collection studies.
- Conduct hybrid data collection studies when possible, addressing evaluation and validation of clinical and usability requirements, including use-related risks. Aim to capture typically difficult and elusive data points, e.g., use-related risk mitigations addressed by "knowledge tasks".
- Employ the realism of real-world settings in clinical studies, when feasible and appropriate for the validation of your final designs.
- When appropriate (and possible), use a staggered approach for your device design validation process, employing simulated-use data combined with real world data.

Pitfalls:

Global introduction of devices with uniform designs and standard safety information in some cases fail to employ comprehensive risk management approach and assessment for regional adaptations, potentially leading to a decrease in device quality and usability and an increase in safety-related risks on a regional scale.

Good practices:

- Share data amongst global device developments and their teams, e.g., known use problems, use-related risks, effective design mitigations, etc. to avoid missing out on opportunities to enhance product usability, quality, and safety.
- Exercise the same degree of scrutiny in the design of regional adaptations and their respective "information for safety" as in device master record (DMR).

Phase 5: Market Introduction and Post-Market Surveillance

Pitfalls:

Post-market activities are frequently viewed as solely regulatory compliance tasks, missing and/ or often ignoring the potential for leveraging and maximizing use-related opportunities and risk data derived from real-world settings.

Good practices:

- Coordinate and synchronize Post-Market Clinical Follow-up (PMCF) and post-market surveillance activities (PDP/HFE) within PDP between HFE, clinical evaluation, and regulatory teams to enhance the integration of (post-market) feedback into subsequent generations of (your) devices.

Conclusion

In this paper, we highlighted the ongoing practical challenges within the HFE process to combine risk-based and user-centered design thinking and approaches and to merge such into the PDP. We showed how such challenges have affected the early and successful integration and execution of an iterative use-related risk analysis and we presented a framework outlining its pitfalls and providing best practices to resolve such.

Additionally, we detailed how the evolution of industry standards and regulations have necessitated the collaboration between human factors and clinical specialists. We illustrated how this collaboration can facilitate the collection of hybrid data for the parallel assessment of usability and clinical evaluation requirements, including use-related risks, and how such an approach could potentially result in more robust data that optimize residual and benefit-risk analyses, facilitate comprehensive development documentation, and strengthen HFE and clinical evaluation processes and reporting.

Key takeaways of our proposed framework:

- **Start early!** An early integration of use-related risk analysis into the PDP, HFE and clinical evaluation, is key for successful and effective planning and subsequent validation, and aids in the prevention of unmitigated risks and the late detection of design deficiencies.
- **Collaborate!** Applying a collaborative approach between HFE and clinical specialists will lead to more robust data, and optimized analysis of use-related risks and benefit-risk analyses. It will also facilitate the development of comprehensive documentation, and strengthen HFE and clinical evaluation processes and reporting.
- **Be transparent!** Share knowledge and data amongst development teams and within the community to allow for the advancement of safer and more effective and usable products, as well as aid in the continuous learning amongst practitioners.
- **Communicate!** The continuous progression of technology will necessitate the ongoing evolution and adaptation of development tools and processes. Therefore, it is imperative to continue the critical discussion on use-related risk analysis, including its early integration and execution within the PDP, and ensure both, HFE and clinical specialists, participate within it.

Lastly, not only could such a framework and cross-functional collaborative approach furnish the manufacturer with a data set that could be utilized for the advancement of potential further risk mitigation and the development of future device (generations), but it could also potentially provide additional advantages, such as improved decision making, better quality control, and enhanced patient outcomes.

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