Response to comments on Comment on Jaki et al. "A proposal for a new PhD level curriculum on quantitative methods for drug development"

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We thank Krause and colleagues [[1]] and Burger [[2]] for the extremely supportive comments to our proposal for a PhD curriculum in drug development [[3]]. Their comments clearly highlight the high need for fit for purpose training in drug development at PhD level and support the multi-faceted approach taken in our proposal. Moreover, the increasing demand for these highly qualified researchers in the light of the evolving landscape of drug development has been well articulated by Burger [2].

How to best train young researchers in evolving statistical methodology such as adaptive designs [[4],[5]], dose finding [6,7,8] and analysis methods [9,10,11]? Traditionally, universities play a central role in the conception and implementation of students training. Academic institutions are the most experienced to propose and run well-designed teaching programmes. However, as pointed out by both comments – and how our proposal for a new PhD programme on quantitative methods for drug development is conceptualized – strong involvement of other stakeholders in the construction and execution of such a new PhD programme is key for a successful and sustainable implementation. Public-private partnership is essential to tailor to the needs of all stakeholders, to enlarge the possible experiences and to facilitate application of the newly developed approaches. For this, the pharmaceutical industry and regulatory agencies will play a key role. The growing demand in industry has been highlighted in [2] while the latter also has an accumulated demand for highly-trained statisticians [12,13,14]. The European Medicines Agency (EMA) established its Biostatistics working party only 10 years ago [15] and its creation has resulted in substantial additional recruitment of statisticians within regulatory bodies. Thus there is a growing demand for graduates of such a quantitative programme in both industry and within regulatory agencies. This high demand was also experienced in the H2020 funded project IDEAS ("Improving Design, Evaluation and Analysis of early drug development Studies"): all former IDEAS students found new posts immediately after completion of their studies – most of them in the pharmaceutical industry. The transfer of knowledge between academia, regulatory agencies and industry will help to raise the acceptance and willingness to implement novel designs and methods faster.

We note with great interest the parallels drawn to the development of Pharmacometrics and certainly welcome close collaboration, as we believe Pharmacometrics is an indispensable part of drug development. Consequently, a solid understanding of Pharmacometrics is crucial for quantitative drug developers making this an essential aspect of any training programme in this field. In the IDEAS programme this is reflected in several of the research projects working on topics within Pharmacometics [16,17]. In our proposal this is recognised in several formal training courses that capture (some) of the areas of Pharmacometics. The dedicated course on Pharmacological modelling has been identified explicitly in the comments, but of course other aspects of Pharmacometrics are captured elsewhere as well. Modelling techniques are ubiquitous throughout the course programme (e.g. dose-finding, Statistical methods for research and preclinical development) and simulation would be a core element of the advanced computational skills training. We do, however, appreciate that further expansion of these areas and links between the disciplines are desirable. For that purpose, it may be useful to develop additional post-graduate level certifications in Pharmacometrics and Quantitative drug development to further supplement the proposed programme and existing Pharmacometrics programmes, respectively.

Last but not least, the name of such a PhD programme is an important factor. It will decide how many and which type of students will be attracted to enrol in such a program. We especially enjoyed the recollection by Krause et al. [1] on which labels have been used for the field of Pharmacometrics over the last decades. We recognize that "curriculum on quantitative methods for drug development" might leave some room for improvement and are open for suggestions and ideas for further collaborations.

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References

[1] Krause A, Kloft C Huisinga W, Karlsson M, Pinheiro J, Bies R, Rogers J, Mentré F, Musser B. (2019) Letter to the editor. *Pharmaceutical Statistics*.

[2] Burger HU (2019) Comment on the paper "A proposal for a new PhD level curriculum on quantitative methods for drug development". *Pharmaceutical Statistics*.

[3] Jaki T, Gordon A, Forster P, Bijnens L, Bornkamp B, Brannath W, Fontana R, Gasparini M, Hampson LV, Jacobs T, Jones B, Paoletti X, Posch M, Titman A, Vonk R, Koenig F (2018). A proposal for a new PhD level curriculum on quantitative methods for drug development. *Pharmaceutical Statistics*, 17(5), 593-606.

[4] Bauer P, Bretz F, Dragalin V, König F, Wassmer G. (2016). Twenty-five years of confirmatory adaptive designs: opportunities and pitfalls. Statistics in Medicine. 35(3), 325-347.

[5] Niewczas J, Kunz C, König F. (2019) Interim analysis incorporating short- and long-term binary endpoints. Biometrical Journal. Early View. https://doi.org/10.1002/bimj.201700281

[6] Yin J, Paoletti X, Sargent DJ, Mandrekar SJ (2017). Repeated measures dose-finding design with time-trend detection in the presence of correlated toxicity data. *Clinical Trials*. 14(6):611-620.

[7] Mozgunov P, Jaki T. (2019) An information-theoretic Phase I/II design for molecularly targeted agents that does not require an assumption of monotonicity. *Journal of the Royal Statistical Society - Series C.* 68(2):347-367

[8] Thomas M, Bornkamp B, Seibold H (2018). Subgroup identification in dose-finding trials via model-based recursive partitioning. *Statistics in Medicine*. 37(10):1608-1624.

[9] Nhacolo A, Brannath W (2018). Interval and point estimation in adaptive Phase II trials with binary endpoint. *Statistical Methods in Medical Research.* Early View. https://doi.org/10.1177/0962280218781411

[10] Mielke J, Innerbichler F, Schiestl M, Ballarini NM, Jones B (2019). The Assessment of Quality Attributes for Biosimilars: a Statistical Perspective on Current Practice and a Proposal. *The AAPS journal.* 21(1):7.

[11] Vradi E, Jaki TF, Vonk R, Brannath W (2018). A Bayesian model to estimate the cutoff and the clinical utility of a biomarker assay. *Statistical Methods in Medical Research.* Early view. https://doi.org/10.1177/0962280218784778

[12] Skovlund, E. Statisticians in European regulatory agencies. Pharm. Stat. 8, 259–263 (2009).

[13] Eichler, H. G. et al. The risks of risk aversion in drug regulation. Nature Rev. Drug Discov. 12, 907–916 (2013).

[14] Bauer, P., & König, F. (2014). The risks of methodology aversion in drug regulation. Nature Reviews Drug Discovery, 13(5), 317.

[15] https://www.ema.europa.eu/en/committes/working-parties-other-groups/chmp/biostatistics-working-party

[16] Erhardt EM, Ursino M, Biewenga J, Jacobs T, Gasparini M (2018). Bayesian knowledge integration for an in vitro–in vivo correlation model. *Biometrical Journal*. Early view. https://doi.org/10.1002/bimj.201700263

[17] La Gamba F, Jacobs T, Geys H, Ver Donck L, Faes C (2018). A Bayesian K-PD model for synergy: A case study. Pharmaceutical Statistics. 17(6):674-684.