

# First-in-Human Drug Evaluation at PRA Health Sciences & the Revised EMA Guideline on Early Clinical Trials

In July 2017, the European Medicines Agency (EMA) published its revised guidance on first-in-human (FIH) and early clinical trials, effective February 2018 (CHMP 2017). The revision provided detailed guidance to identify risks to trial participants that arise from uncertainty associated with the medicinal product tested and mitigate risks in trial design and conduct. The EMA's guidance update considered that early clinical trial protocols have become increasingly complex and that protocols often include multiple parts and objectives. The revision was triggered at least in part by recent unexpected serious adverse reactions in the early clinical development setting, despite significant regulations.<sup>1-2</sup>

PRA Health Sciences was one of many stakeholders providing input to the cooperative effort to draft this guideline revision.

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## What does the revised EMA guideline imply for FIH trials in PRA?



PRA's approach to clinical drug development has always prioritized science and safety. The EMA guideline update has not changed PRA's approach to safe and informative early clinical development programs, including FIH studies. The publication of the July 2017 guideline revision has not affected timelines or approval efforts of submitted clinical trial applications (CTAs) for studies executed by PRA.

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## How does PRA implement the revised EMA guideline for FIH trials?



The clinical study protocol is the key document that addresses the revised guideline's provisions. Well-written protocols comply with applicable guidance for protecting the safety and wellbeing of participants and producing strong scientific outcomes. The revised guideline also provides latitude for justified alternative study design approaches to be considered on a case-by-case basis:





Alternative Study Design	Details
Sentinel Dosing	Sentinel dosing is typical for the first single ascending dose (SAD) cohort of an FIH study. PRA recommends assessing additional SAD cohorts on a case-by-case basis and eliminating sentinel groups when justified (eg, by absence of severe or irreversible toxicity for which a sentinel safety biomarker is not available, a wide margin between the maximum exposure in animals and in the FIH study, and expected absence of non-linearity of pharmacokinetics [PK]). Justification for excluding sentinel dosing in multiple ascending dose (MAD) studies may include preclinical evidence of the absence of increased risk after repeated dosing (eg, absence of (near)-irreversible target binding, absence of structural changes in target organs or other delayed effects, and absence of severe or irreversible toxicity for which a sentinel safety biomarker is not available).
Starting dose and dose escalation	Starting dose and dose escalation are defined in the protocol based on the relationship between targeted exposure in the FIH study, exposure with significant toxicity observed preclinically, and projected efficacious clinical exposure. Dose escalation decisions are based on emergent safety data and, as justified on a case-by-case basis, on PK and pharmacodynamic (PD) data. The size of escalation steps is dictated by emerging data and the steepness of the relationship between dose/exposure and toxicity. If multiple dosing data indicate tolerance to adverse effects seen in the SAD phase, higher exposures in the MAD phase may be considered.
Supra-therapeutic exposure	Supra-therapeutic exposure in early trials is essential for evaluating the exposure-effect relationship for QTc; identifying the plateau of a biomarker; and collecting information on the anticipated safety and tolerability profile in patients with unintended high exposure (eg in liver or kidney failure, or due to drug interactions). Protocol justification text addresses the anticipated therapeutic and supra-therapeutic exposure range based on preclinical data, as well as the absence of severe, irreversible toxicity without sentinel safety biomarker in preclinical studies at exposures near the maximum targeted exposure in the FIH study.
Stopping and halting criteria	Stopping and halting criteria guide and monitor dose escalation and repeated dosing, and mitigate risk by establishing checks in the protocol with actual safety, PK (exposure), and/or biomarker data or (preliminary) efficacy data. These criteria typically comprise assessments indicated by the preclinical package (eg, types of adverse events, laboratory findings, and/or biomarker and exposure information evaluated in a consistent, rolling safety review process).
Integrated protocol	Integrated protocols, including multiple study parts and objectives in FIH studies, are commonly performed by PRA and are endorsed by the EMA guidance. Studies may include a SAD and MAD component, a food-effect component, and a drug-interaction component. Although some components may overlap if justified in the protocol, continuation to a next part is based on predefined criteria and a review of all available data.

PRA includes these justifications in a structured risk assessment<sup>3</sup> that identifies and minimizes risk and provides the basis for designing safe, expedited trial designs tailored to the product's needs.

#### References and further reading

1. van Iersel MT. The use of IC<sub>50</sub> for potency and MTD as objective in Study BIA 10-2474. *J Clin Pharmacol*. 2017a;57:1357-1358.
2. Van Hoogdalem EJ. Take Care of the Fast-in-Human Study. *Clin Transl Sci*. 2017;10:122-123
3. van Iersel MT, Greenberg HE, Westrick ML. Structured risk assessment for first-in-human studies. *Ther. Innovation Regulatory Sci*. 2017b;51:288-297
4. Chaikin P. Reply to Letter: The Use of IC<sub>50</sub> for Potency and MTD as Objective in Study BIA 10-2474, by Mattheus van Iersel, MD. *J Clin Pharmacol*. 2017;57:1359-1361.
5. Committee for Medicinal Products for Human Use (CHMP). Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/07 Rev. 1. 20 July 2017.
6. DeGeorge J, Robertson S, Butler L, Derzi M, Stoch SA, Diaz D, Hartke J, Guzzie-Peck P, Mortimer-Cassen E, Bogdanffy M, Will Y, Greene N. An Industry Perspective on the 2017 EMA Guideline on First-in-Human and Early Clinical Trials. *Clin Pharmacol Ther*. 2017 Dec 29. doi: 10.1002/cpt.984.
7. Ponzano S, Blake K, Bonelli M, Enzmann H; European Medicines Agency Committee for Human Medicinal Products "First-in-Human Guideline Drafting Group". Promoting Safe Early Clinical Research of Novel Drug Candidates: A European Union Regulatory Perspective. *Clin Pharmacol Ther*. 2017 Nov 6. doi: 10.1002/cpt.899.

## Next Steps

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