Sentinel Dosing—Time for a Risk-Based Approach?

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On behalf of the ACCP Public Policy Committee

Is it time to reconsider the broad and empirical requirement for sentinel dosing in early clinical trials and move toward a more rational, risk-based approach in early drug development? Let us start by laying out the initial arguments that provoked broad-scale implementation of sentinel dosing. In March 2006, eight male volunteers enrolled in a first-in-human (FIH) trial for a CD28 superagonist monoclonal antibody, TGN1412. This monoclonal antibody was designed to paradoxically co-stimulate the immune system via T-cell activation to induce immune tolerance. In what was standard practice then, six volunteers were randomized to receive active drug and two were randomized to receive a placebo. Volunteers were dosed sequentially at 10-min intervals, with each intravenous infusion lasting 3 to 6 min. Volunteers received a starting dose of 0.1 mg/kg. Nearly immediately following the infusion, volunteers started to report severe headaches, fever, and lower back pain. Volunteers were restless with nausea and vomiting. Soon after, the subjects became hypotensive and developed an exaggerated systemic inflammatory response hallmarked by severe tissue swelling consequent to massive vascular leak syndrome. One volunteer went into marked respiratory distress and was moved into the hospital's intensive care unit. All remaining volunteers were moved to the intensive care unit as a precaution. Some volunteers required ventilatory support; all volunteers required blood transfusions. All volunteers remained in intensive care for approximately 1 month, except for one volunteer who remained in the unit for more than 3 months.[1] Two years later, volunteers that received the experimental antibody still had sequelae from the incident. All had memory difficulties, three were diagnosed with mild-to-moderate depression, and one required amputation of finger digits resulting from gangrene and persistent Reynaud's disease.[2]

Shortly after the incident occurred, an investigation was launched by the expert scientific group on Phase 1 trials by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). It was not known at the time what caused the incident. Hypotheses included dose contamination, sabotage, and dosing errors. Within 3 weeks, the MHRA issued an interim report, commonly referred to as the Duff Report after the name of the senior author.[3] The report concluded that the volunteers suffered from "life-threatening cytokine release syndrome," or more euphemistically known as a cytokine storm, where the immune system overreacts to immune stimulation releasing large amounts of cytokines into the blood from immune cells. The report concluded that it "did not involve errors in the manufacture of TGN1412 or in its formulation, dilution or administration to trial participants" and that the effects were an adverse event of the immune-stimulating effects of TGN1412 itself. The report also concluded that the adverse events were "unpredictable." This conclusion has been particularly controversial, with most experts believing this consequence was, in fact, a likely drug overdose outcome since preclinical safety data and the chosen FIH dose, which nearly saturated the intended receptor, were not understood by the sponsor.[4,5]

Nevertheless, after TGN1412, changes were instituted on the conduct of FIH Phase 1 studies to prevent such a tragedy in the future. One recommendation of

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the Duff Report was an appropriate period between dosing individual volunteers. In the TGN1412 study, there was only a 10-min interval between dosing volunteers. Other recommendations included the use of the Minimum Anticipated Biological Effect Level (MABEL), the lowest human dose that is likely to produce a measurable biological effect, as the starting dose for future FIH studies.[6] In 2007, the European Medicines Agency (EMA) issued its first guidance on how to identify and mitigate risk in FIM studies.[7] One of the recommendations that EMA made was that within each cohort one volunteer should receive active drug with an "adequate period of observation" between the first and subsequent administrations to the remaining volunteers (section 4.4.2.4). Such a design element has been called "sentinel dosing." An "adequate period of observation" is not defined in the guidance, although the guideline states that the interval must be justified and depends on the properties of the drug and all available data. Typically, however, this can involve at least 1 day of separation between dose administration in the first and subsequent volunteers.

In 2017, the EMA Guidance was updated,[8] after another Phase 1 trial tragedy occurred with BIA 10–2474, a fatty acid amide hydrolase (FAAH) inhibitor being developed for neuropathic pain by Portugal's Bial Pharmaceuticals, after 5-6 days of multiple dose administration of 50 mg QD. In this instance, however, there were fatal results.[9] The fatality and other SAEs were likely due to the relative non-specificity of BIA 10–2474 for FAAH inhibition and off-target effects for other cerebral hydrolases. It has also been hypothesized that BIA 10—2474 might indiscriminately alkylate non-target tissue.[9] Other FAAH inhibitors in development by Pfizer, Merck, and Janssen did not have significant safety outcomes in their Phase 1 trials.

The updated FIH EMA Guidance uses the term "sentinel dosing" and expands its use to include two sentinel volunteers, one of which receives active drug and the other receives placebo, when the study design includes placebo patients. Sentinel dosing may continue or start at subsequent higher dose levels when receptor occupancy may be high, nonlinear pharmacokinetics may occur, or when emerging safety signals may occur. At the end of each dosing cohort, all available data should be reviewed before enrolling volunteers at a higher dose level. Notably, other regulatory agencies, like the US Food and Drug Administration and Japan's Pharmaceuticals and Medical Devices Agency, have not issued any guidance related to this topic. However, anecdotal evidence indicates that the US Food and Drug Administration does require or recommend sentinel dosing in FIH studies in many circumstances. To add to the confusion surrounding this topic, Institutional Review Boards (IRBs) may recommend or require sentinel dosing for approval of FIH trials, with a lack of uniformity by local and central review boards and without similar requests from the FDA. These indiscriminate mandates increase the uncertainty, time, and cost of early clinical trials and the overall cost of clinical development, which is a major driver in the pricing of new drugs. These requests may come from IRBs less experienced with early trials and may be driven by the false sense of security that sentinel dosing offsets a thorough preclinical assessment of the drug candidate's risks.

Although the EMA Guidance provides flexibility in the timing of the doses between the sentinel volunteers and the rest of the cohort, it does not provide flexibility in whether the sentinel volunteers must always be employed. It broadly treats all drugs the same, and all drugs should have sentinel dosing for FIH studies during both the SAD and MAD periods.

But is this strict mandate necessary? Are there more conditions where a sentinel cohort is unnecessary? Instead, should sentinel dosing be justified? Could a risk-based approach be used to determine whether a sentinel dose is used? Certainly, the safety of the volunteers enrolled in any clinical trial is paramount. But all drug candidates do not carry equal risk. For example, does a prodrug of an already approved drug warrant sentinel dosing? Does the development of a single enantiomer version of an already approved racemic drug warrant sentinel dosing? These are just a few obvious conditions where sentinel dosing should not be universally warranted, and this also depends on the totality of preclinical data available to enable an integrated assessment of risks to healthy volunteers in FIH trials. An inflexible mandate inevitably adds unnecessary delays, cost, and patient burden.

To bring these risks into perspective, the number of Phase 1 clinical trials from 2012 to 2022 increased from 1232 to 2162, with an estimated 150,000 volunteers for Phase 1 trials in 2021 alone[10] (Figure 1). Yet the number of major incidents as reported has been extremely low, a testament to the overall safety of the processes of bringing a drug to the clinic for the first time. A previous study on the risk to patient in Phase 1 trials reported a median of zero severe adverse events (SAEs) per 1000 treatment group participants/day of monitoring from 475 trials enrolling 27,185 participants.[11] A more recent study from a Pfizer-owned clinical research unit reported that "*among 11,028 healthy participants who received study drug in non-oncology phase I studies, 34 (0.31%) experienced serious adverse events, with no life-threatening events or deaths reported. Of the 34 serious adverse events, 11 were related to the study drug and seven to study procedures, whereas 16 were unrelated to a study drug or procedure, including four that occurred when the participant was receiving a placebo*."[12]

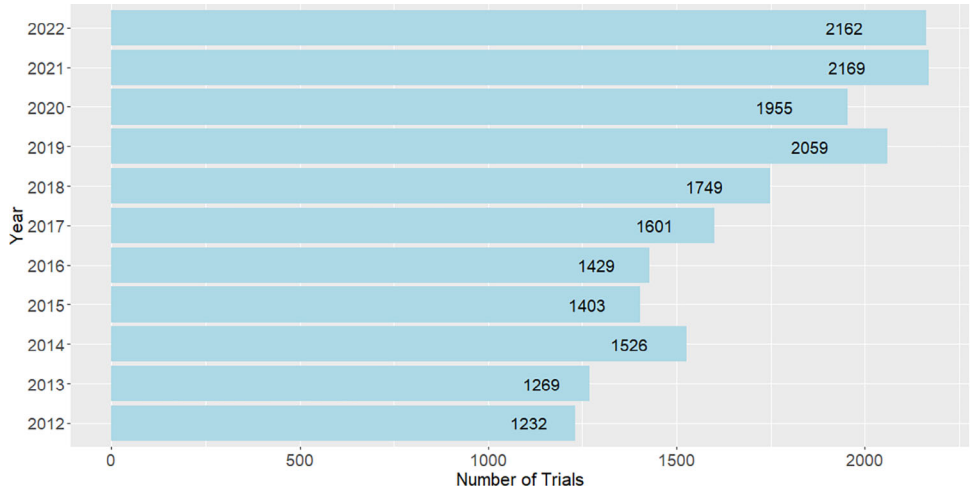

Figure 1. Number of Phase 1 studies worldwide between 2012 and 2022. Figure redrawn from reference [10].

We propose that drug developers and government regulators take a risk-based approach in determining whether sentinel dosing is necessary for a Phase 1 drug candidate instead of a blanket approach for all drug candidates entering FIH studies. This would demand early scientific discourse on the need for sentinel dosing by the key parties. Recommendations for drugs that would require sentinel dosing could include:

- Novel mechanism of action.
- In certain cases, novel modalities.
- Low specificity for intended target or lack of information regarding inter-species differences in on-target versus off-target effects.
- Qualitative differences in metabolism between animal species used in toxicity testing versus humans (i.e., presence of human unique metabolite(s)).
- Steep dose/concentration–response profile.
- The desire/need to identify maximum tolerated dose (MTD) in healthy volunteer FIH trials versus risk/benefit considerations.
- Inadequate confidence in the relevance of animal species used in toxicity testing.
- Lack of sufficient safety (exposure) margins at no adverse event level (NOAEL) in relevant species for toxicity testing versus expected highest human exposure; type and reversibility of toxicity are equally important considerations.
- Parenterally administered drugs where intervention to mitigate toxicity is difficult (vs orally administered drugs).
- Drug candidates that may have a narrow therapeutic index.
- Drug candidates that irreversibly bind to the intended target or have the potential, as parent or metabolite, to covalently bind.
- Situations where no in vitro or in vivo models predict human target cell/tissue response or outcomes.
- Toxicity in animals that is not monitorable in humans.

It is recognized that this is not an all-inclusive list nor ranked in order of importance; rather, the aspects that are delineated are based on rational preclinical and clinical pharmacology principles (leading up to FIH trials); the aspects include drug candidates, target patient populations, and other relevant considerations. Preclinical programs should enable an integrated evaluation of human risks in healthy volunteers in FIH trials, and the need for sentinel dosing should be based on such evaluations.

A simple, empirical position is to follow a strategy that is "better to be safe than to be sorry." In the case of TGN1412, sentinel dosing would have been appropriate since it checks some of the boxes delineated in the proposed list shown above. However, the individual receiving the sentinel dose would have experienced life-threatening consequences and therefore, a catastrophe would not have been averted. Yet, had a single volunteer been dosed with TGN1412 prior to the rest of the cohort, those latter patients would have been spared significant pain and irreversible damage. With the Bial trial, however, the catastrophe unfolded on Days 5 and 6 of the MAD study cohort and safety events did not uniformly affect all dosed subjects.[9] In this case, it is unclear if sentinel dosing would have mitigated the outcome. In contrast, the probability of a SAE TGN1412 was 100% with the chosen FIH dose since this dose virtually saturated the intended target receptors, triggering the cytokine storm.

But let us consider an alternate scenario. If a drug candidate has an SAE probability of 50%, there is only a 1 in 2 chance of seeing the SAE with the sentinel cohort of two subjects. With a 10% SAE rate, this

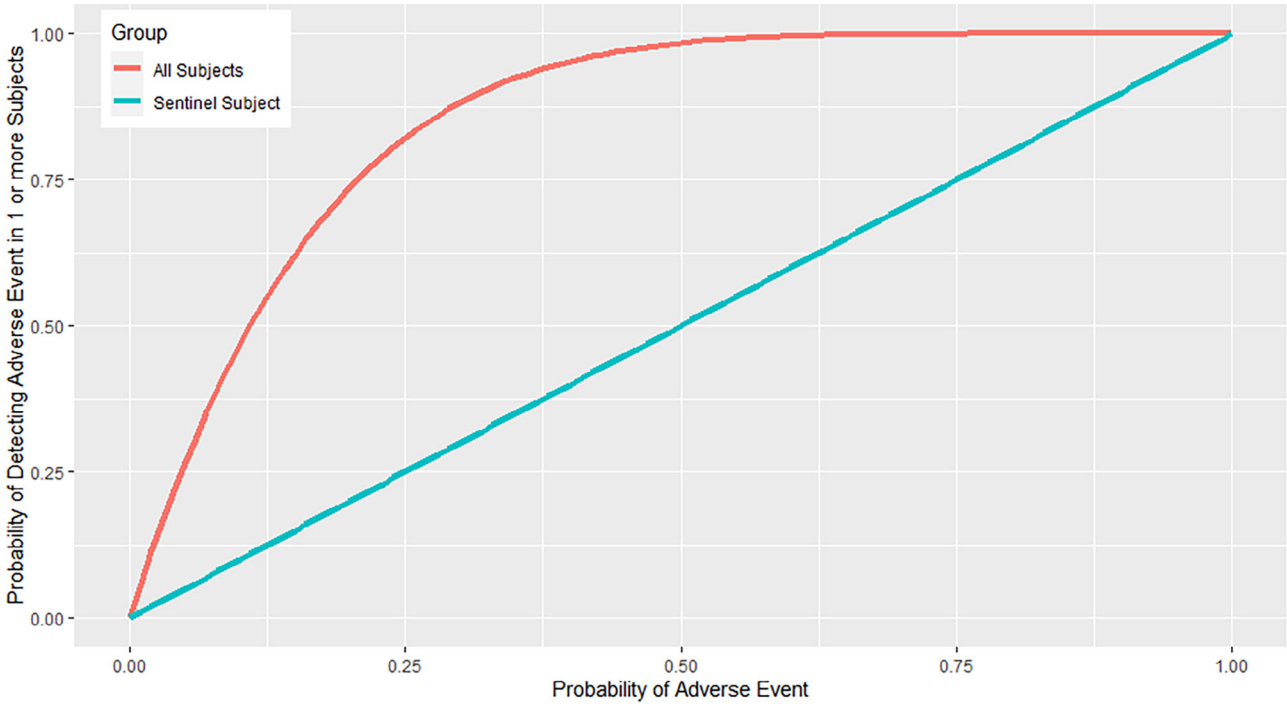

Figure 2. The probability of detecting an adverse event in the sentinel volunteer or across all volunteers (n = 6) as a function of the true probability of the adverse event occurring in the population.

decreases to only a 1 in 10 chance; hence, even with six subjects in a sentinel group, the chances of seeing the SAE in one or more volunteers is only about 1 in 2 (Figure 2). Senn[13] reports that in the 1990s, the Phase 1 SAE rate ranged from 1.9% to 7.6%. More recent estimates suggest that Phase 1 studies may be safer today. Johnson et al.[11] reported that in an analysis of 475 Phase 1 clinical trials with healthy volunteers, the median rate of mild and moderate adverse events was 1147 and 46 per 1000 volunteers, respectively. The median incidence of SAEs was 0% with a total of 15 events across 9747 volunteers. The likelihood of seeing an SAE in Phase 1 trials is practically zero. This can give rise to a false sense of security with sentinel dosing when no adverse events are seen in the sentinel cohort. Appropriate dose selection/escalation strategies with integrated evaluation of human risks and more rigorous safety monitoring may be the more prudent approach to safer Phase 1 dosing as a general rule.

In conclusion, we propose that government regulators, ethics committees, and drug developers employ a risk-based approach in determining the need for sentinel dosing with more scientific discourse devoted to the most informative and safe strategy for Phase 1 drug development and consider a more upstream (i.e., preclinical mechanistic safety) derisking of new drug candidates using a better understanding of their mechanism of action, metabolism, off-target binding, and other properties that may impact their effect.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

Not applicable.

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