These days, people live longer. A fact generally accredited to higher standards of living, improved self-awareness of a healthy life-style and also, importantly, better healthcare. For example, life expectancy in the USA has increased by more than 30 years in the last century, 25 years of this gain being attributable to public health benefits [1]. There is an enormous amount of medicine available for patients, ranging from cough medicine to complex chemotherapy drugs for cancer patients. The number of products, ‘distinctive medicines, described by brand or generic name, or both’ [2], listed in the physicians’ compendia in 1981 were 2100 in the UK and 6000 in the USA [3]. Currently, the pharmaceutical industry in the EU, Japan and the USA follow the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines [101] to conduct tests on medicines in preclinical trials and clinical trials before they can be granted a license by regulatory authorities.

In preclinical trials, a new compound is tested on animals (in vivo) or cells (in vitro). Its toxic responses are monitored along with pharmacological aspects: pharmacokinetics – drug concentrations in the body (cell), and pharmacodynamics – drug reactions in the body (cell), targeting certain molecules or receptors and the potentially efficacious response of the drug. Once the compound has been proven safe and has potential efficacy, it will be administered into humans to test the safety and efficacy further.

Phase I clinical trials are used to establish the safety of the drug when it is first administered into humans. An identified safe dose from preclinical studies is scaled for human subjects, either by body weight or body surface area [4]. This will form the starting dose (x) for a Phase I trial. A fixed dose range will be used. Usually it is based on a doubling scale (x, 2x, …) or a modified Fibonacci sequence (x, 2x, 3.3x, 4.95x, …) [5]. Each dose of this fixed range is to be tested for its safety. In cancer trials a typical study design is a parallel group, randomized and conducted on a small number of subjects, for example, 20–80. Subjects are randomly allocated into two groups: one is the treatment group (to receive the new active compound) and the other one is the control group (either to receive a placebo or an existing compound). Dose-escalation procedures either follow a predefined rule or are based on clinicians’ judgment. An example of a predefined rule is the ‘3 + 3’ up-and-down rule [6]: each treatment group contains three subjects. If no toxicity is observed within three patients, then the next group of subjects will get the next higher dose. If one out of three patients had toxicity, then the same dose will be repeated for the next group. If more than two out of three patients had toxicity, then the trial will...
be stopped. A dose-toxicity response curve will be identified at the end of the trial. The maximum tolerated dose (MTD) associated with a certain percentage of dose-limiting toxicity will be calculated.

As long as a Phase I trial does not stop at the first dose, a Phase II trial can be planned, to seek evidence for efficacy of the drug. Several treatment groups will be used, such as low, medium and high dose groups (with all doses below the MTD). From these different dosages, usually only one potential efficacious dose will be carried into Phase III trials, where the drug and the dosage are tested on large numbers of patients for a long time to thoroughly check the efficacy. If the response of people who received the dose is statistically significantly different from that of people who received a control, then investigators will be able to submit their findings to the relevant regulatory agency (e.g., US FDA and European Medicines Agency) for an approval of a license. Once a licence is granted and the medicine is manufactured, its long-term side effects will be monitored (this is the Phase IV stage of a clinical trial).

From an investigator’s point of view, clinical trials are lengthy and expensive. Hence, the following question is very important: how many dose levels should be used in Phase I trials? Too many dose levels are not ideal: first it could cost too much to manufacture different doses, and second it would take longer to test each of them. From a patient’s point of view, however, ‘one dose for all’ is neither ethical nor feasible. It would raise the question ‘how could a patient know that they are in conformity with the population that the dose was tested on?’ In fact, there have been many medicines withdrawn or the dosage modified as a consequence of such considerations [7]. Patients would like to see as many dose levels as possible to be tested in Phase I trials and more than one dose to be compared in Phase III trials. Therefore, there is a fine balance between investigators willingness to spend money and patients requirements.

First and foremost, new scientific dose-finding methods should be employed to help investigators shorten the length of Phase I trials. Bayesian adaptive designs have been increasingly used instead of predefined rules since the 1990s [8–10]. These are model-based methods. They take into account previous knowledge (either similar compound, the preclinical data of the compound or clinicians experience) of the dose-response curve and treat it as a priori. With certain utility functions (e.g., give the next group of people the estimated MTD or give the next group of people a dose that will maximize the accuracy of the estimated model), the dose-escalation procedure recommends an optimal starting dose. This dose does not need to be the lowest available dose. This is ethically appealing as the lowest dose could be non- efficacious. After observing responses from the first group of subjects, the initial dose will be updated to derive an updated optimal dose for the next group of subjects. The procedure will be repeated until some predefined stopping rules are reached (e.g., if the maximum number of subjects has been reached). Some doses on the fixed-dose range may be skipped during the dose-escalation procedure if they were not recommended as optimal doses. These skipped doses are either non- efficacious or too toxic. Thus, skipping doses certainly provides a quicker way to conduct Phase I trials compared with the traditional nonskipping dose-escalation rules. Some Bayesian adaptive methods even incorporate subjects’ effect into the model so that appropriate doses will be recommended to individual patients based on their responses so far in the trial [11,12]. Since Bayesian adaptive methods are model based, they provide more accurate estimates of the MTD [12].

The next question is: how many dose levels should be used? How can investigators be sure that the fixed-dose range they are considering is the right range? Some trials have to be rerun as they fail to identify the MTD in the original dose range. Here, computer simulation programs can help investigators to identify better dose ranges [13]. In simulations, several scenarios can be set up. Bayesian adaptive designs are applied to these scenarios. After multiple simulations, outputs display how often dose levels had been skipped, which dose has been identified as the optimal dose at the end of simulations and how accurate these results are. Based on this information, investigators can modify the dose range (e.g., shorten the dose range, take away too low non- efficacious doses and too high toxic doses and expand the range around the optimal dose to fine tune the dosage). Then they can run more simulations and adjust the new dose range and dose levels further. Simulations can be lengthy and require specialist knowledge of the methodology behind the designs and programming. However, they match ethical requirements, as they are not running on human subjects and reduce the risk of putting real human subjects on nonefficacious or high-toxic doses later in a real study. They provide more accuracy of the estimates of the optimal dose and dose-response curves, which will have a knock-on effect: if the dose range and dose levels are more accurately identified in Phase I trials, this will increase successful rates of Phase II trials and lead to more successful Phase III trials. This, in the long run, will therefore be cheaper than a badly planned trial.

Bayesian adaptive designs and simulations are not easy to understand and run. They require statisticians, programmers and clinicians to work closely together. All aspects of the design (how to set up priors, choose utility functions and scenarios, and so on) need to be discussed before a real trial can be run. Simulations should be
conducted at the discussion stage to help finalize the design. The recommendations of optimal doses in the real trial should be checked and sometimes overruled by clinicians if they have any concerns of safety [14].

Bayesian adaptive designs have a bright future in the drug development. Pharmaceutical companies and research institutions have applied some designs in real studies [15,16]. There is a working group on adaptive dose-ranging studies in the Pharmaceutical Research and Manufacturers of America. The objectives of the group are ‘to develop new and evaluate existing adaptive dose-ranging methods, and to produce policy recommendations for regulatory agencies on their use in clinical drug development’ [17]. In the FDA guidelines [102], there is a specific session on adaptations for exploratory dose-selection studies, which discusses possibilities of adding ‘new potentially more preferable doses’ rather than just eliminating ‘unsuitable or uninformative doses’. With the help of scientists, dose-finding studies should play a more important roles. Patients will benefit from more accurate doses and investigators should also benefit from more successful studies.

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