How First-Time-in-Human Studies Are Being Performed: A Survey of Phase I Dose-Escalation Trials in Healthy Volunteers Published Between 1995 and 2004

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First-time-in-human studies are small, time-lagged dose-escalation studies including volunteer subjects evaluating safety and tolerability. There is little consensus in the design of a first-time-in-human study, and it is difficult to get an overview of studies performed. One hundred five studies comprising 3323 healthy volunteers published in the 5 major clinical pharmacology journals since 1995 were analyzed. The average trial was placebo controlled, double blind including 32 subjects at 5 dose levels but with great variation in cohort size and dose-escalation method. The parallel single-dose design was the most common design, with the crossover designs being more frequent in the early publications. Despite discussions on the optimization of phase I trials, little seems to be happening. The development of study designs and evaluation methods for cancer trials is extensive, but formal statistically based methods and more scientific study designs are unusual in phase I dose-escalation trials in healthy volunteers.

Keywords: *Phase 1; first-time-in-man; healthy volunteers; dose escalation; new safe medicines faster*

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First-time-in-human studies, sometimes called first human dose studies or first-in-man studies, are the first clinical studies performed as a part of a phase I drug development program and the very first time the investigated substance is administered to humans. The first-time-in-human studies are traditionally small, time-lagged, dose-escalation studies including volunteer subjects, and the primary objective is the identification of a suitable dose or dose range for further study, based on the safety and tolerability of the substance.

Phase I studies are critical in the overall process of drug development. This phase is a key point at which the bridge from animal to human studies occurs, and the studies offer the first opportunity to investigate the drug in humans. There are many uncertainties and much to be taken into consideration when planning and executing a first-time-in-human study. It is an ample opportunity to learn as much as possible as early as possible, and if the study is appropriately designed and evaluated, there is a great deal of information to collect, even in a small study.

In the past decade, there has been much focus on the optimization of early drug development, and many articles advocating the need of formalization of phase I studies and the implementation of more statistically based designs have been published.[1-5] Within cancer research, formal statistical methods such as the continual reassessment method[6] are being used today, and there is hope that the methods developed in the cancer area can be modified and applied to dose-escalation trials in other therapeutic areas and studies involving healthy volunteers. The opportunity to collect more information early in the development phase can lead to a shortened development time and reduced develop-

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ment costs. But to optimize phase I trials, one must first understand how they are being performed today.

Today, there appears to be as many methods of conducting first-time-in-human studies as there are pharmaceutical companies and scientific and academic institutions, and the method chosen is more a result of habit and preference than a well-founded scientific and statistical rationale. There seems to be no consensus on how to perform first-time-in-human studies in healthy volunteers, and, as expected not all phase I studies are published[7]; it is difficult to get an overall picture on the world of first-time-in-human studies.

The objective of this article is to outline the detailed design of all phase I dose-escalation trials involving healthy volunteers published in the 5 major clinical pharmacology journals during the past decade to show what phase I dose-escalation studies are being performed and how. We hope this might give a foundation for discussion and debate on the design of first-time-in-human studies.

METHODS

Five major clinical pharmacology journals, *British Journal of Clinical Pharmacology*, *Clinical Pharmacology and Therapeutics*, *European Journal of Clinical Pharmacology*, *International Journal of Clinical Pharmacology and Therapeutics*, and *Journal of Clinical Pharmacology*, were selected and scanned for publications of phase I dose-escalation trials (first-time-in-human studies). All issues published in the 10-year period from January 1, 1995, to December 31, 2004, were examined manually, and the articles were selected based on title and abstract.

The selection criteria were phase I dose-escalation studies involving healthy volunteers. If the identified study was not a first-time-in-human study and the actual first-time-in-human dose-escalation study had been published elsewhere, this study was recovered and included in the analysis. If the identified study were indeed the first published dose-escalation study (eg, preceded by a small pilot study, whether published or not), it was included in the analysis, but had the study been preceded by a larger phase I study or an unpublished dose-escalation trial, the study was excluded from the analysis. The method resulted in the identification of 105 studies published in 72 articles.

The studies were then analyzed based on therapeutic area, size, blinding and control, study design, dose escalation, cohort size, and distribution of subjects within the cohorts. Of the phase I dose-escalation studies included in the analysis, most were published in 1 of the 5 selected journals. Only 4 of the studies were published in other journals and identified based on references.

As control, an advanced MEDLINE search was performed searching for articles published since January 1995 with titles/abstracts containing the phrases *phase 1, phase I, healthy volunteers*, or *safety* and *tolerability*, excluding all cancer trials. The search resulted in 2707 hits, 98 of which were judged to be phase I dose-escalation studies based on title and/or abstract. Based on the control, it is sufficient to conclude that the 72 articles recovered from the 5 journals are representative of the overall publication of phase I trials in the selected time period.

RESULTS

A total of 72 publications comprising 105 studies and representing 50 different organizations/institutes were recovered from the 5 international journals and identified as phase I dose-escalation trials in healthy subjects (Table I). Eighty-five of the 105 studies were absolute first-time-in-human studies. All major therapeutic areas were represented in the studies; grouping the studies according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system, 11 of the 14 groups at level 1 were represented (all but dermatologicals, sensory systems, and varia; Table II). At level 2 of the ATC classification system, the 105 studies could be sorted into 28 subgroups, with the largest group, analgesics, containing 11 studies and 6 groups containing only 1 study.

The distribution over time of the studies published in the period studied is illustrated in Figure 1. A large majority (86 studies; 81.9%) of the studies were placebo controlled, and 66 (62.9%) of them were double blind. Eleven of the studies (10.8%) were single blind, 13 were open, and for 15 of the studies (14.7%), the degree of blinding was not stated in the publication. The studies comprised a total of 3323 healthy volunteers ranging from 108 to 4 subjects per study (Figure 2); the average number of subjects in a study was 31.65, and the median was 28.

The studies show a great variation in the cohort sizes and distribution of subjects within the cohorts. The cohorts consisted of 2 to 16 subjects, with 30 as the extreme exception in 1 study.[59] The most abundant cohort size was 8 subjects, usually with 6 subjects allocated to active treatment and 2 to placebo, a distribution implemented in 29 of the studies. Figure 3 displays the distribution of subjects within the cohorts for the studies and the number of studies in which the particular distribu-

(text continues on p. 1128)

Table I Outline of the Design Details for the 105 Phase I Dose Escalation Trials Identified by the Survey

Reference Number	Placebo	Blinding	Number of Subjects	Cohort Size	Cohort Distribution	Dose Levels	Dose Increments,[a] %	Organization
Parallel single-dose studies								
8	Yes	Open	27	9	6 + 3	3	108-100	Pharmos Corporation
9	No	Open	24	6	6 + 0	4	150-100	Bayer
10	No	Not stated	23	5	5 + 0	5	150-33	Yoshitomi
11	Yes	Double blind	24	6	4 + 2	4	600-100	Vertex Pharmaceuticals
12[b]	No	Open	24	4	4 + 0	7	100	Yamanouchi
13	No	Open	39	3	3 + 0	9	900-100	Orion Pharma
14	Yes	Double blind	16	8	6 + 2	2	50	DuPont Merck
14	Yes	Double blind	32	4	3 + 1	8	500-25	DuPont Merck
15	Yes	Double blind	88	8	6 + 2	11	100-25	Hoechst Marion Roussel
16	Yes	Double blind	19	3	2 + 1	4	100-50	Dr Willmar Schwabe Arzneimittel
17	No	Open	12	4	4 + 0	3	233-200	Hamamatsu University
18	No	Open	6	2	2 + 0	3	100	Hoffmann-La Roche
18	Yes	Double blind	18	6	4 + 2	3	43-20	Hoffmann-La Roche
19	Yes	Double blind	56	8	6 + 2	7	233-33	Pharmacia & Upjohn
20	Yes	Double blind	32	8	6 + 2	4	150-50	Rhône-Poulenc Rorer
21	Yes	Not stated	24	8	6 + 2	3	100	Zeria
22	Yes	Single blind	56	8	5 + 3	7	100-25	Viro Pharma
23	Yes	Not stated	40	6	6 + 2	5	233-61	Novo Nordisk
24	No	Open	28	3	3 + 0	7	150-100	Universities of California and Turku
25	Yes	Double blind	40	8	6 + 2	5	300-33	Aventis
26	Yes	Double blind	31	4	3 + 1	6	400-100	Merck
27	Yes	Single Blind	28	6	4 + 2	4	100-50	Seoul National University
28	Yes	Double blind	48	8	6 + 2	6	150-100	Hoffmann-LaRoche
29	No	Not stated	18	6	6 + 0	3	400-700	Zeneca
30	Yes	Double blind	108	9	6 + 3	10	100-10	Merck
31	Yes	Double blind	24	6	5 + 1	4	900-133	Abbott
32	Yes	Double blind	40	8	5 + 3	5	100	Sankyo Pharma
32	No	Open	34	6	6 + 0	6	100	Sankyo Pharma
33	Yes	Double blind	62	8	6 + 2	8	150-48	Novo Nordisk
34	Yes	Double blind	48	8	6 + 2	6	300-100	Novo Nordisk
35	No	Not stated	24	6	6 + 0	4	100-33	Kitasatu University
36	Yes	Double blind	32	4	3 + 1	8	233-20	CeNeS Pharmaceuticals
37	Yes	Not stated	16	8	6 + 2	2	33	Hamamatsu University
37	No	Not stated	10	2	2 + 0	4	233-200	Hamamatsu University
38[b]	Yes	Double blind	80	16	10 + 6	5	200-33	Pfizer
39	Yes	Not stated	30	6	5 + 1	5	400-100	Idun Pharmaceuticals
40	Yes	Double blind	42	6	5 + 1	5	200-50	Wyeth
41	Yes	Double blind	56	8	6 + 2	7	300-50	Johnson & Johnson

(continued)

Table I (continued)

Reference Number	Placebo	Blinding	Number of Subjects	Cohort Size	Cohort Distribution	Dose Levels	Dose Increments,[a] %	Organization
42	Yes	Double blind	56	8	6 + 2	7	100-50	Novo Nordisk
43	Yes	Double blind	28	7	5 + 2	4	186-75	Eisai Research Institute
44	Yes	Double blind	56	8	6 + 2	7	100-33	Chiesi Farmaceutici
45	Yes	Double blind	48	8	6 + 2	6	400-33	Novo Nordisk
46[b]	Yes	Double blind	63	9	6 + 3	7	233-100	Bristol-Myers Squibb
47	Yes	Double blind	25	5	4 + 1	5	114-100	Hammersmith Medicines Research
48	Yes	Not stated	57	8	6 + 2	7	100-25	Yamanouchi
49	Yes	Double blind	56	8	6 + 2	7	233-33	Pharmacia
50	Yes	Double blind	32	8	6 + 2	4	233-200	GFI Pharmaceutical Services
50	Yes	Double blind	80	8	6 + 2	9	233-33	GFI Pharmaceutical Services
51	Yes	Double blind	32	4	3 + 1	5	300-100	MDS Pharma
52	Yes	Single blind	30	6	4 + 2	5	67-33	Yuhan
Parallel multiple-dose studies								
53	Yes	Double blind	24	8	6 + 2	3	100	Dr Willmar Schwabe Pharmaceuticals
54[b]	Yes	Double blind	40	10	8 + 2	4	100-33	Sanofi
15	Yes	Double blind	32	4	3 + 1	8	100-33	Hoechst Marion Roussel
32	Yes	Double blind	30	10	7 + 3	3	100	Sankyo Pharma
34	Yes	Double blind	32	8	6 + 2	2	100	Novo Nordisk
34	Yes	Double blind	24	8	6 + 2	3	300-100	Novo Nordisk
35	No	Not stated	12	6	6 + 0	2	100	Kitasatu University
55[b]	Yes	Double blind	50	10	8 + 2	5	400-33	Wyeth-Ayerst
56[b]	Yes	Double blind	64	16	12 + 4	4	100	Merck
39	Yes	Not stated	30	6	5 + 1	5	400-100	Idun Pharmaceuticals
45	Yes	Double blind	24	8	6 + 2	3	700-300	Novo Nordisk
46[b]	Yes	Double blind	45	9	6 + 3	5	150-50	Bristol-Myers Squibb
57[b]	Yes	Double blind	32	8	6 + 2	4	100-50	BIAL
47	Yes	Double blind	18	6	4 + 2	3	114-100	Hammersmith Medicines Research
48	Yes	Not stated	40	10	8 + 2	4	100-50	Yamanouchi
52	Yes	Single blind	16	8	6 + 2	2	100	Yuhan
58[b]	Yes	Double blind	39	9	6 + 3	4	100-33	Bristol-Myers Squibb
59[b]	Yes	Double blind	60	30	20 + 10	2	300	Novartis

Alternating crossover studies								
60[b]	Yes	Double blind	8	4	3 + 1	19	100-9	Bristol-Myers Squibb
60[b]	Yes	Double blind	9	3	3 + 3	19	100-9	Bristol-Myers Squibb
61[b]	Yes	Double blind	24	12	Not stated	8	100-20	Rhone-Poulenc Rorer
16	Yes	Double blind	24	12	Not stated	4	200	Dr Willmar Schwabe Arzneimittel
21	No	Not stated	4	2	2 + 0	4	100	Zeria
62	Yes	Double blind	16	8	6 + 2	8	150-33	Zambon Group
63	Yes	Single blind	19	9	9 + 9	6	233-33	Pfizer
64	Yes	Double blind	12	12	8 + 4	3	100	AstraZeneca
Crossover studies and grouped crossover studies								
9	Yes	Double blind	14	7	Not stated	2	300	Bayer
53	Yes	Double blind	12	12	9 + 3	6	100-40	Dr Willmar Schwabe Pharmaceuticals
65	Yes	Not stated	8	8	8 + 8	6	100-95	University of Chicago
61[b]	No	Open	16	16	16 + 0	2	100	Rhone-Poulenc Rorer
66	Yes	Single blind	16	8	6 + 2	6	100-25	Janssen Research Foundation
67[b]	Yes	Double blind	8	8	8 + 8	3	200	Yamanouchi
68	Yes	Single blind	16	8	6 + 2	6	100-25	Janssen Research Foundation
69	Yes	Double blind	14	8	6 + 2	3	100-50	Orion Pharma
69	No	Open	18	3	3 + 0	14	100-13	Orion Pharma
70[b]	Yes	Single blind	8	4	4 + 4	5	900-100	SmithKline Beecham
63	Yes	Double blind	16	4	4 + 4	4	100-33	Pfizer
63	Yes	Single blind	11	10	10 + 10	4	233-200	Pfizer
63	Yes	Single blind	9	9	9 + 9	3	50-34	Pfizer
71	Yes	Double blind	9	9	6 + 3	6	50-17	Wyeth-Ayerst
Parallel single- and multiple-dose studies								
72[b]	Yes	Double blind	60	10	8 + 2	6	100-20	SmithKline Beecham
61[b]	Yes	Double blind	36	12	Not stated	3	100	Rhone-Poulenc Rorer
16	Yes	Double blind	27	14	11 + 3	2	100	Dr Willmar Schwabe Arzneimittel
73	Yes	Double blind	48	12	8 + 4	4	400-100	Glaxo Wellcome
71	Yes	Double blind	36	9	6 + 3	4	100-20	Wyeth-Ayerst
74[b]	Yes	Double blind	36	12	8 + 4	3	100-50	Abbott
Idiosyncratic studies								
75	No	Open	17	8	8 + 0	2	100	Pharmacia & Upjohn
75	No	Open	17	2	2 + 0	7	100	Pharmacia & Upjohn
76	No	Open	8	2	2 + 0	4	400-100	Ferring
77	Yes	Single blind	25	5	4 + 1	10	200-33	Astra
58[b]	Yes	Double blind	11	11	7 + 4	3	100	Bristol-Myers Squibb
10	No	Not stated	9	9	9 + 0	3	50-33	Yoshitomi

a. The escalation increments are reported in percentages. If the increments varied throughout the dose escalation, the largest and the smallest increments are reported.
b. Not a first-time-in-humans study.

Table II Therapeutic Areas Explored in the Investigated Studies Grouped According to the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System

ATC Group	ATC Subgroup	Number of Studies
Alimentory tract and metabolism	Acid related disorders	2
	Antiemetics	2
	Bile and liver therapy	2
	Drugs used in diabetes	2
	Other	2
Blood and blood-forming organs	Antianemic preparations	3
	Antithrombotic agents	7
	Other	4
Cardiovascular system	Antihypertensives	6
	Cardiac therapy	2
	Renin-angiotensin system	6
Genito urinary system	Sex hormones	1
	Urologicals	9
Systemic hormonal preparations	Pituitary and hypothalamic hormones	1
Anti-infectives for systemic use	Antivirals	3
Antineoplastic and immunomodulating agents	Immunosuppressive agents	2
Musculo-skeletal system	Anti-inflammatory products	1
	Bone diseases	7
Nervous system	Analgesics	11
	Antiepileptics	4
	Psycholeptics	2
	Antiparkinson drugs	1
	Psychoanaleptics	7
	Other	9
Antiparasitic products	Anthelmintics	1
	Ectoparasticides	1
Respiratory system	Antihistamines	2
	Obstructive airway diseases	5

tion is applied. In 4 of the studies,[9,16,61] the distribution of active and placebo-treated subjects was not stated in the article.

The dose-escalation scheme did also vary between the studies. The number of dose levels investigated in the studies ranged from only 2 up to 19, with most (86.7%) of the studies investigating 7 dose levels or fewer (Figure 4). The average number of dose levels used in the studies was 5.24, and the median value was 5.

Various dose-escalation schemes were employed in the studies. They could be categorized as linear, logarithmic, modified Fibonacci, or miscellaneous, including escalation regimens in which the 3 standardized methods are combined. A linear escalation method, in which the dose increment is fixed, is used in 12 of the studies. Twenty-two of the studies used a logarithmic dose-escalation scheme, in which the relative dose increment is the same, for example, 100%. The modified Fibonacci escalation method is frequently used in cancer phase I trials[3,78-80] and has also to some extent been implemented in phase I dose-escalation trials in healthy volunteers; 4 of the studies are using a modified version of the Fibonacci sequence. However, most (67 studies, or 63.8%) of the dose-escalation schemes reported do not seem to follow one particular model. Some are a combination of 2 of the models described above (eg, starting with a logarithmic escalation to convert into a modified Fibonacci sequence), while for other studies, there is no apparent scheme and the doses seem to be arbitrarily chosen.

Five major study design types could be identified among the studies (Table I, Figure 5). In the most common parallel single-dose design (Figure 5a), each subject receives only 1 administration of 1 dose. The doses are gradually escalated, and after each dose administration and subsequent safety evaluation, a new cohort

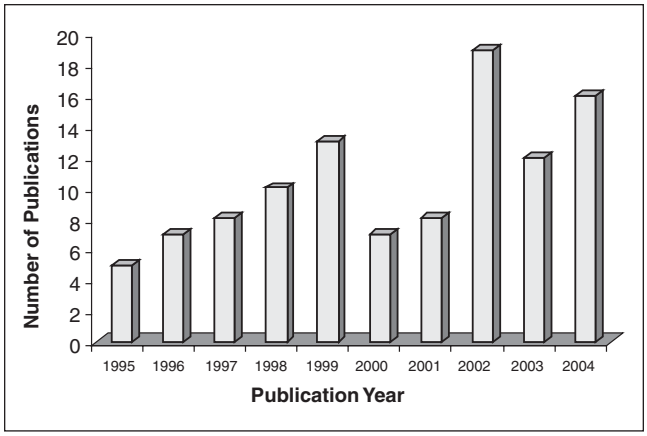

Figure 1. Number of phase I dose-escalation studies published in the 5 major clinical pharmacology journals since 1995.

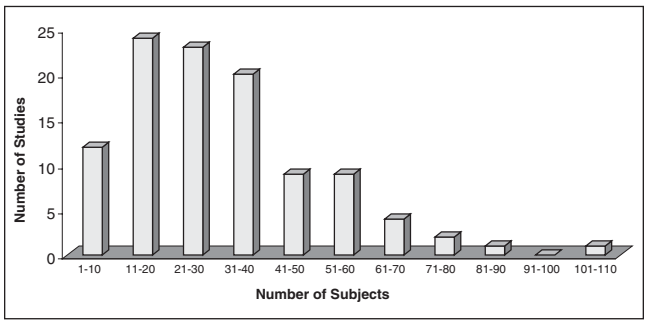

Figure 2. Total number of subjects included in the studies investigated.

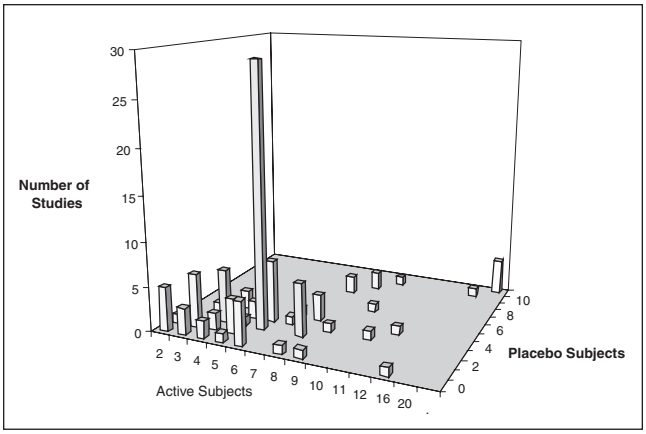

Figure 3. The distribution of subjects within the cohort. The light gray pillar represents the 4 studies in which the distribution of subjects was not stated in the article.

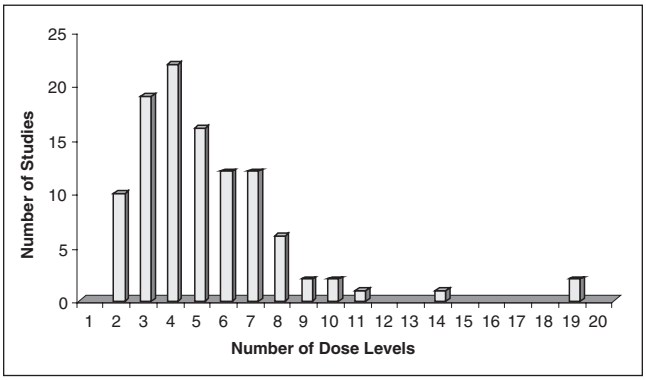

Figure 4. The number of dose levels investigated in the studies.

with new subjects is included and administered the next dose. A variation of this design is the parallel multiple-dose design (Figure 5b), in which the subjects are administered multiple doses at the same dose level. But again, a new cohort is included for each dose level. The parallel single- and multiple-dose design (Figure 5c) is a combination of the 2 previously described. After the safety evaluation, which generally is based on single-dose data from more than 1 dose level, the single dose is followed by a multiple administration of the same dose within the same cohort. In the crossover studies, each subject receives various dose levels of the substance. In the grouped crossover studies with 1 or more dose groups, the doses are crossed within each group (Figure 5d). All subjects within a cohort receive the same doses in the same order, and a placebo is randomized among the drug administrations. Between each dose administration, there is a safety evaluation and a washout period. The number of groups, number of dose levels within a group, and the cohort size in the group can vary. In the alternate crossover design, the dose escalation is alternated between 2 or more groups (Figure 5e). Each group receives every other (or third, etc) dose, and during the dosing of one cohort, the other cohort(s) are in washout. Within the cohort, placebo administration can be randomized, either to the same person throughout the study or in a rotating manner.

Six of the studies were not possible to characterize, either because the exact subject allocation was not reported in the article[75,77] or because an idiosyncratic design was applied.[10,58,76]

The parallel single-dose design was the most recurrent among the designs identified, implemented in 52 of the 105 studies (49.5%). Nineteen (18.1%) of the studies were parallel multiple-dose studies (Table I).

The studies with a more elaborate design, with several different doses administered to each subject, were less frequent. Eight studies (7.8%) could be categorized as alternating crossover studies, 14 (13.7%) were grouped crossover studies with 1 or more groups, and 6

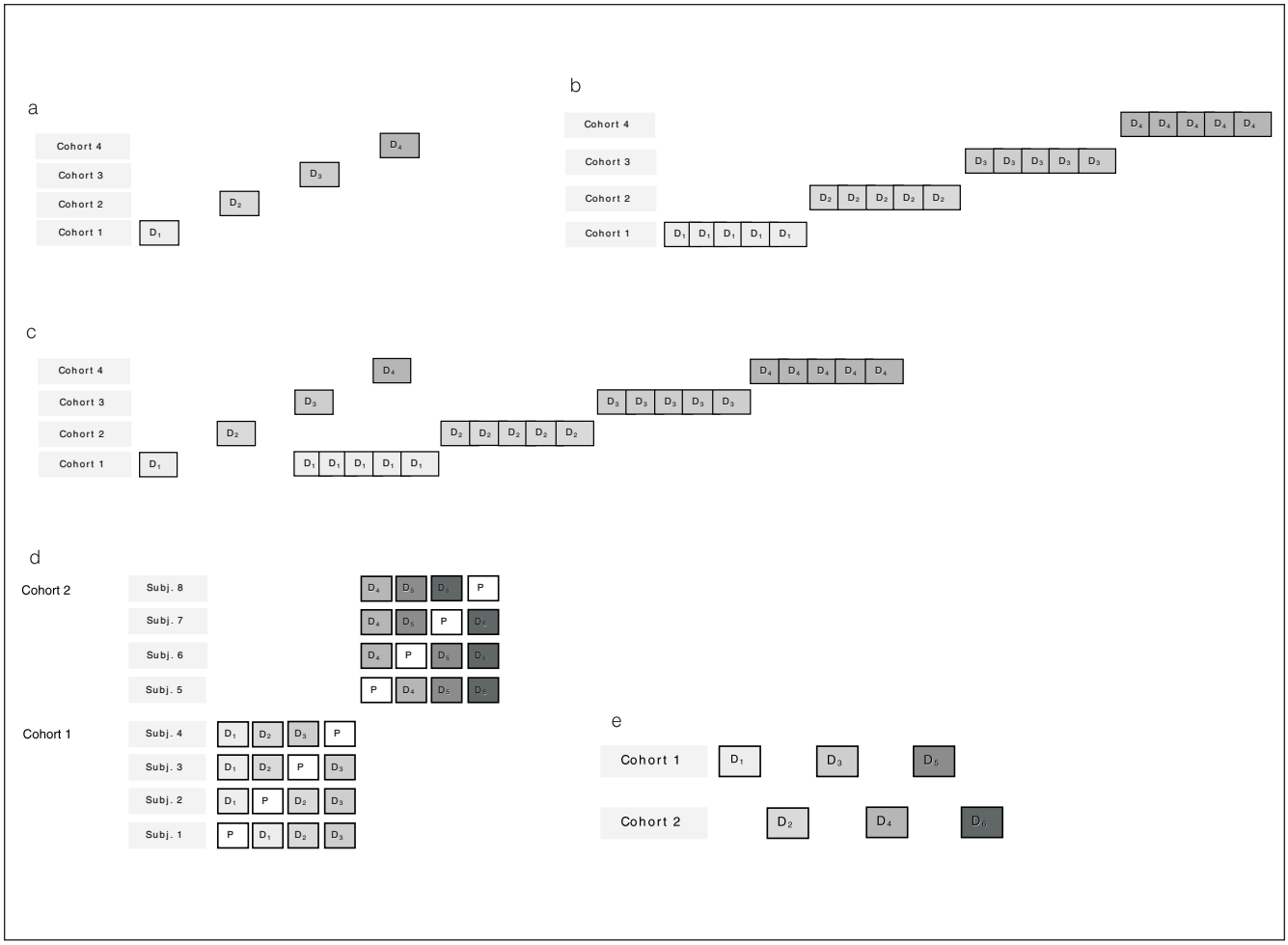

Figure 5. Five major dose-escalation designs were identified among the studies: (a) parallel single-dose escalation, (b) parallel multiple-dose escalation, (c) parallel single- and multiple-dose escalation, (d) grouped crossover dose escalation, and (e) alternating crossover.

(5.9%) studies were combined single- and multiple-dose escalation studies (Table I).

DISCUSSION

First-time-in-human studies are pivotal in the drug development process; they present the researchers' first opportunity to study the substance in its target species and can present a lot of data if designed appropriately.

The increasing cost of drug development has brought increased focus to processes developed for the purpose of optimizing, rationalizing, and increasing the capacity of and eliminating redundancies in clinical trials without compromising safety. The efforts have been collectively gathered under the motto "New Safe Medicines Faster" in Europe and "The Critical Path" in the United States.[81]

The distribution of the studies over the time period illustrated in Figure 1 shows a trend toward an increase in the number of studies published in the most recent years. During the past decade, several articles have appeared that advocate the need for better publication ethics and improved reporting of clinical trials,[7,82-84] and it appears that the number of phase I trials being published is indeed increasing. However, most of the first-time-in-human studies published are still cancer trials, and there exists no record on how many phase I studies are actually being performed; hence, it is not certain whether the observed publication increase is due to an increase in the number of phase I trials performed or actually a result of better publication ethics. Certainly there might be a publication bias in the reporting of first-time-in-human studies, but the many studies published during the past decade should still

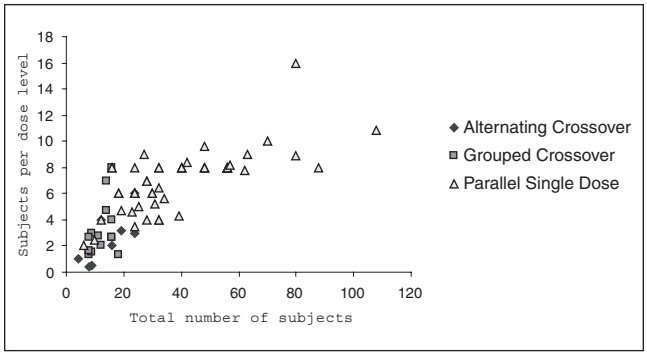

Figure 6. The number of subjects per dose level investigated shown for 3 study designs.

be able to provide an ample image of the way these studies are being performed.

Time delay may be another confounding factor. Many of the studies were performed quite recently prior to publication date, but several were performed a long time before they were published. It might be possible that the studies performed today are different from the studies published today, but as the time period studied is large (10 years) and little has changed during this period, the survey should provide a representative picture of the modern first-time-in-human studies.

The studies investigated were sponsored by both industry and academia, and the study designs differ just as much within the 2 groups. Most of the studies are double blind, and only for a small percentage of the studies is there no information on the degree of blinding. But 15 studies is still too much, and as even the small phase I trials investigated here are clinical trials, the blinding should be reported in the publication.

The use of placebo in phase I trials has been debated,[85-87] but the majority (82%) of the first-time-in-human studies are placebo controlled. Of the 19 that are not, only 3 studies involved 28 subjects or more; most of the studies that were not placebo controlled were thus relatively small studies.

There was a large variation in the number of subjects investigated in each trial, but with the average number of subjects just exceeding 30 and most of the studies (77%) involving 40 subjects or fewer, it is clear that the studies are small and manageable. Of course, the total number of subjects in a dose-escalation trial depends on the number of dose levels investigated, but when looking at the number of subjects per dose level for the studies investigated (Figure 6), although there is still much variation (from 0.42 subjects per dose level to 16), in 74% of the studies only 8 or fewer subjects are tested per dose level.

Despite the small studies and the small cohorts, almost every possible combination of active and placebo treatments within a cohort is implemented. In light of the disparity, 1 combination comes through as the most abundant. There seems to be some consensus around the 6 + 2 distribution, which is applied in 29 studies. The use of at least 6 active subjects has been recommended,[88] and it is comforting to see that although the studies are small, the cohorts are large enough to yield conclusive data. The small size of the first-time-in-human studies results in reduced power and predictability. Thus, it is important to adapt the design of the studies to obtain as much and as reliable information as possible. By increasing the cohort size by just 1 or 2 subjects, there is much to gain in power and detectability, especially if the cohort size is very small (fewer than 6 subjects).[88]

The number of dose levels investigated seems to have no connection with the escalation scheme employed, and most of the studies do not appear to follow any particular escalation scheme. Instead, the entire dose escalation seems rather arbitrarily based on starting dose and stopping dose, with the other dose levels spread out in between.

The starting and stopping doses chosen depend on safety and toxicology preclinical data and are expected to be quite individual based on substance, therapy area, animal models, and method of starting dose selection. There are several publications discussing the optimal starting dose selection,[89,90] and the US Food and Drug Administration has issued a draft guidance[91] on the estimation of the starting dose. But once the starting dose is selected, by whichever method chosen and based on the preclinical data, the actual escalation scheme will determine which and how many doses are administered.

The modified Fibonacci escalation is frequently used in cancer trials to allow for a rapid escalation in the lower doses and a more moderate escalation in the higher doses, and it seems to be gaining ground in ordinary phase I trials as well. The dose escalations in cancer phase I trials are moving toward more formal methods[92,93] including the continual reassessment method,[6] in which the doses administered are based on the results from the previous dose levels. The demands on a regular phase I trial with healthy volunteers are not as high as on a cancer phase I trial involving patients, but the formal methods developed for cancer trials can be considered as an illustration of what can be achieved in any first-time-in-human study and can perhaps promote the development of similar, but more complex, methods for studies in healthy volunteers.

Within the 11 therapeutic areas investigated in the studies, all 5 major study designs were represented.

The largest ATC group was "nervous system," with 34 studies within 6 subgroups (Figure 7a). As exemplified by the nervous system, the distributions of the designs were evenly spread within most of the therapeutic areas. The only exception was "blood and blood-forming organs," and antithrombotic agents in particular (Figure 7b). Of the 14 studies in substances affecting blood and the blood-forming system, 13 were parallel, and 12 were parallel single dose. The largest subgroup was anticoagulants, with 7 parallel single-dose studies. The absence of crossover designs in this group can be explained by the concern for carryover effects; when studying an anticoagulating drug, the outcome of too high a plasma concentration could be fatal, and one wants to avoid any risk of carryover effects.

Of the 5 major study designs identified, the parallel single-dose design was the most frequent within all therapeutic areas; it was applied in almost half of the 105 studies. But it is also the most conservative design, with each subject receiving 1 administration of only 1 dose, and with the traditional parallel design, one cannot directly differentiate intrasubject variability from intersubject variability, as is possible if the substance is administered on more than 1 occasion. The crossover designs—grouped crossover and alternating crossover—take a more novel approach and allow for the investigational product to be administered more than once to each subject. They allow for more information to be obtained from fewer subjects and are more efficient in estimating dose proportionality.[94-96]

Yin and Chen used mixed-effect modeling to evaluate first-time-in-human design alternatives for their precision in estimating dose proportionality,[97] and they concluded that an alternate design always requires fewer subjects to achieve the same precision compared to a sequential design. This is also the case in the studies investigated here. In Figure 6, the number of subjects per dose level is depicted for the parallel single-dose studies, the crossover studies, and the alternating crossover studies. The number of subjects needed per dose level and also the total number of studies varies greatly, but it is evident that for parallel studies, the number of subjects included in the studies is much larger than for the 2 other designs.

There might be some inclination toward viewing the 2 latter (crossover and alternating crossover studies) as the more experimental and preferable studies, as they allow for more information to be gathered using fewer subjects, thus saving both time and money. However, looking at the publication timeline for the 3 study designs, this is not the case. Most of the studies are parallel single-dose studies, and they seem to be increasing

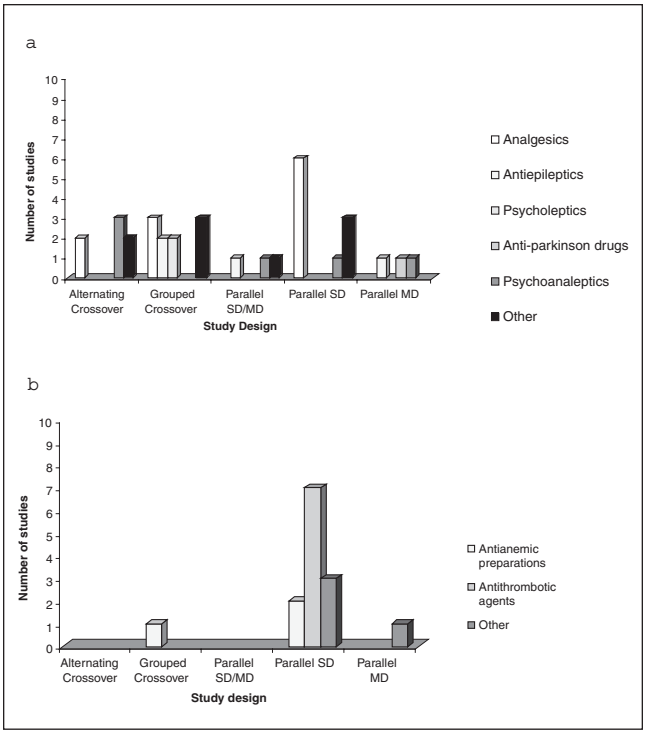

Figure 7. The study designs employed were evenly distributed within the therapeutic areas, exemplified here by the largest group, the nervous system (a). The only exception was for substances affecting the blood and blood-forming organs, in which all studies save 1 were parallel (b). SD = single dose; MD = multiple dose.

rather than decreasing. In Figure 8, the 3 studies are compared over the time period studied; for clarity, the 2 crossover designs are viewed together as "novel designs."

It appears that the experimental novel study designs were more frequent in the past, and most of the newly published studies are of traditional parallel design. The reasons for this might be many, including practical and logistical reasons such as volunteer recruitment/interest in relation to multiple revisits to the clinical unit; fear of carryover effects, as noted for the antithrombotic agents; or packaging and randomization of clinical drug supply. However, it seems that despite ongoing discussions on "new safe medicines faster" and "optimizing phase I trials," phase I dose-escalation trials are still conservative and seem to be based more on habit and preferences than experimental and scientific rationale.

The development of study designs and evaluation methods for first-time-in-human cancer trials has been extensive in the past years, and this might also rub off on first-time-in-human studies in healthy volunteers. In cancer trials, the formal statistically based methods

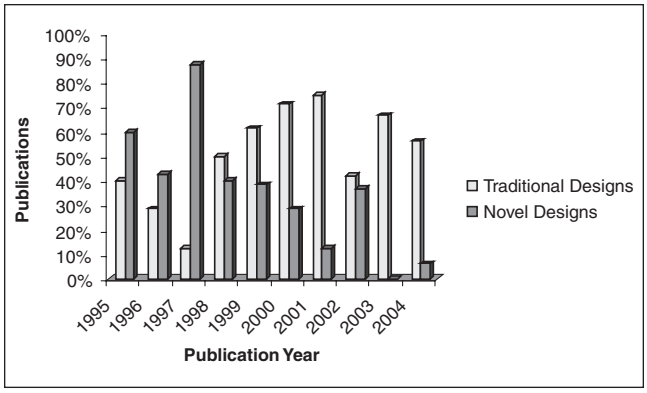

Figure 8. Allocating the studies into 2 groups illustrates the development of phase I trial designs. Despite the fluctuation, it is evident that the traditional trials are increasing at the expense of the novel, more exploratory designs.

are gaining ground, and the future for dose-escalation trials in healthy volunteers looks bright. With open minds, extended power calculations, and methods adding more statistical rationales to these trial designs, we will be able to optimize phase I trials and develop our new safe medicines faster.

CONCLUSIONS

The design of first-time-in-human studies in healthy volunteers seems to be very arbitrary. There is great variation in number of dose levels, escalation methods, cohort sizes and distribution, and treatment allocation. The majorities of the designs are conservative and seem to be based on habit and preference instead of the statistical and scientific rationale needed to optimize the first-time-in-human studies. With a good overview of the way the trials are performed today, there is a base for continued discussion on the design of first-time-in-human studies in healthy volunteers.

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