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## Bioequivalence and Bioavailability Clinical Trials: A Status Report from the National Institutes of Health [ClinicalTrials.gov](http://ClinicalTrials.gov) Registry

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### Abstract

Drug development is an expensive process that is marked by a high-failure rate. For this reason early stage bioequivalence and pharmacokinetic studies are essential in determining the fate of new drug products. In this study, we sought to systematically assess the current trends of ongoing and recently completed bioequivalence and bioavailability trials that have been registered within a national clinical trials registry. All bioequivalence and bioavailability studies registered in the United States [ClinicalTrials.gov](http://ClinicalTrials.gov) registry from late-2007 through 2011 were identified. Over this period, more than 2300 interventional bioequivalence and bioavailability trials were registered. As of 2013, the vast majority of studies (86%) have been completed, 10% are actively recruiting participants, and the remainder are engaged in data analysis (4%). When compared to completed trials, ongoing trials are in later phases of clinical development, recruiting larger numbers of participants, and more likely to recruit women and children ( $P < 0.001$  for all). These data suggest that the quality of bioequivalence and bioavailability studies has improved rapidly, even over the last five years. However, further work is needed to sustain – and accelerate – these improvements in the design of bioequivalence and bioavailability studies to ensure that safe and efficacious medicines swiftly reach healthcare providers and their patients.

### Keywords

Clinical trials; Biomedical research; Healthcare reform; Pharmaceuticals

### Introduction

Many drug patents have recently expired or are scheduled to expire in the near future [1]. In response, many drug manufacturers have expanded their generic drug portfolio, which requires them to conduct clinical trials that demonstrate that their generic equivalents perform similarly to the innovator drug product [2]. Regulations introduced by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA)

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over the last thirty-five years have strengthened measures to ensure the bioequivalency of drug products, which may be simultaneously manufactured by multiple drug makers [3-5]. Bioequivalence and bioavailability testing standards have also emerged following recognition that bioinequivalence and variations in the bioavailability of drug products can result in therapeutic failure and/or toxicity [6-8].

In the United States, the successful approval of new and abbreviated new drug applications requires regulatory approval by the FDA [9]. Recent studies have suggested that this process takes nearly a decade to complete the required series of pre-clinical studies and clinical trials [10]. Drug development is an expensive process that is marked by a high-failure rate [11]. For these reasons, early stage bioequivalence and pharmacokinetic studies are essential in determining the fate of new drug products.

In this study, we sought to systematically assess the current trends of ongoing and recently completed bioequivalence and bioavailability trials that have been registered within a national clinical trials registry. This study provides insight regarding the characteristics of current bioequivalence and bioavailability trials and may also provide assistance in prioritizing future areas of research.]

## Methods

### Selection of bioequivalence and bioavailability trials

We identified bioequivalence and bioavailability trials registered in [ClinicalTrials.gov](http://www.clinicaltrials.gov) using the key words “bioequivalence” and “bioavailability”. Briefly, [ClinicalTrials.gov](http://www.clinicaltrials.gov) is a publicly-available registry of clinical research studies that is maintained by the U.S. National Institutes of Health. As of mid-2013 there were nearly 150,000 studies registered in [ClinicalTrials.gov](http://www.clinicaltrials.gov), with study sites in 185 countries (<http://www.clinicaltrials.gov>).

Our search was restricted to identify studies registered between 01 October 2007 and 31 December 2012 to coincide with the enactment of a federal law in 2007 that mandated the registration of all phase 2-4 interventional trials involving drugs, biological agents, and medical devices [12]. We excluded all observational trials (n=34) as well as trials that were “suspended” (n=7), “terminated” (n=33), or “withdrawn” (n=26). The remaining trial registry entries were systematically examined and the following data elements were extracted: a unique trial identifier, study title, recruitment status, phase (0-4), study design, blinding status, interventional assignment to trial arms, primary endpoint classification, primary purpose of the trial, age group and gender eligibility criteria, and anticipated enrollment size.

### Statistical analyses

Descriptive statistics were used to characterize the bioequivalence and bioavailability trials identified in the [ClinicalTrials.gov](http://www.clinicaltrials.gov) registry. Comparisons between ongoing trials and those that have been completed were performed using the  $\chi^2$ -test or Fisher’s exact test. Continuous variables were compared with the non-parametric Kruskal-Wallis test. All statistical analyses were undertaken in Stata 11.2 (StataCorp LP, College Station, TX, USA).

## Results

### Trial characteristics

From October 2007 through December 2012 there were 2,388 interventional bioequivalence and bioavailability trials registered in [ClinicalTrials.gov](http://ClinicalTrials.gov). Of these, 227 (10%) trials are actively recruiting participants, 15 (1%) are recruiting by invitation only, 87 (4%) are engaged in data analysis, and 2,059 (86%) have been completed. The 15 most commonly investigated disease states / conditions are featured in Figure 1.

A comparison of ongoing and completed clinical trial characteristics is presented in Table 1. Ongoing bioequivalence and bioavailability trials are more likely to be in later phase clinical trials, as reflected by a decrease in the proportion of phase 0, 1, and 1/2 trials from 75% among completed studies to 36% of ongoing studies ( $P<0.001$ ). Ongoing trials are also more likely to be double-blinded (27% vs. 12%;  $P<0.001$ ) and have larger sample sizes ( $P<0.001$ ). Similarly, ongoing trials are more likely to feature parallel group assignment and less likely to be crossover trials ( $P<0.001$  for both). There has also been an increase in the proportion of trials that primarily involved research on treatments from 42% to 55% ( $P<0.001$ ). The proportion of trials that exclusively recruited male participants declined from 20% to 9% ( $P<0.001$ ) and the number of trials that enrolled children increased from 3% to 17% ( $P<0.001$ ).

### Geographic distribution

More than half of the bioequivalence and bioavailability trials registered in [ClinicalTrials.gov](http://ClinicalTrials.gov) were conducted internationally (58%). Among ongoing trials, 48% are being conducted at sites located outside of North America. The global distribution of ongoing bioequivalence and bioavailability trials is shown in Figure 2. The majority of ongoing trials are recruiting participants in North America (52%) and Europe (26%); however, East Asia (7%), the Middle East (4%), and South America (4%) are also involved in several ongoing bioequivalence and bioavailability trials.

## Discussion

This study reveals that bioequivalence and bioavailability trials are part of a global clinical research enterprise. When compared to completed trials, ongoing trials are in later phases of clinical development, recruiting larger numbers of participants, and more likely to recruit women and children. These data suggest that bioequivalence and bioavailability studies are undergoing a transformation as drug makers seek to characterize the safety and efficacy of drug products in more rigorous trials that closely resemble their anticipated patient population.

As the costs of healthcare and drug development have risen, there is a mounting incentive for improving our understanding of existing treatments while also enabling breakthrough discoveries [13]. Recently, the United Kingdom has attempted to strategically align their clinical research funding with their public health priorities [14]. Although similar measures have not been enacted in the United States, it behooves policy makers to consider the vital role that bioequivalence and bioavailability studies play in bringing new and generic drug

products to the public. As noted here, the quality of bioequivalence and bioavailability studies has improved rapidly, even over the last five years, and the horizon is bright. However, as the national debate on healthcare reform and research priorities unfolds we may need to re-evaluate our approach to bioequivalence and bioavailability trials to ensure that safe and efficacious medicines swiftly reach healthcare providers and their patients.

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## Abbreviations

<b>NIH</b>	National Institutes of Health
<b>NLM</b>	National Library of Medicine
<b>FDA</b>	Food and Drug Administration
<b>EMA</b>	European Medicines Agency

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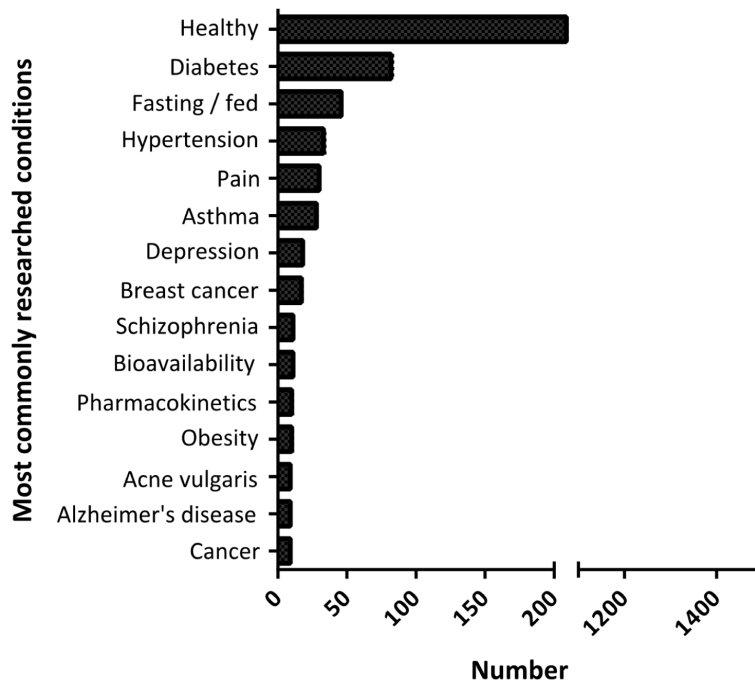
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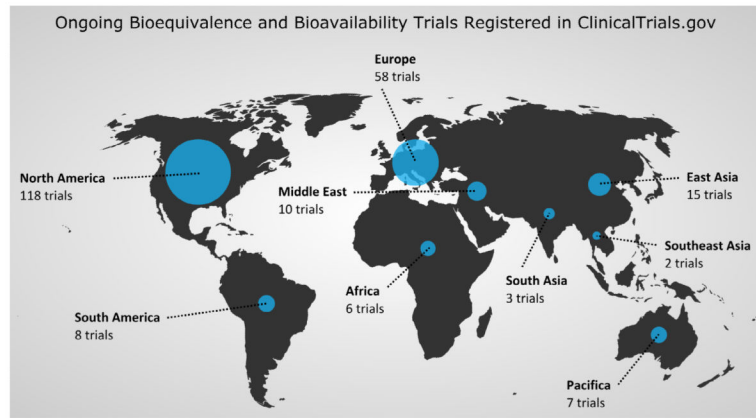
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**Figure 1.** Distribution of the 15 most commonly researched disease states / conditions among bioequivalence and bioavailability studies registered in [ClinicalTrials.gov](http://ClinicalTrials.gov).



**Figure 2.** Global distribution of ongoing bioequivalence and bioavailability trials registered in [ClinicalTrials.gov](http://ClinicalTrials.gov) in 2013. The size of the blue circles denotes the number of ongoing clinical trials within each geographic region.

**Table 1**

Interventional bioequivalence and bioavailability clinical trial characteristics among ongoing and completed trials.

Characteristic	Category	Bioequivalence & Bioavailability Trials	
		Ongoing ( <i>n</i> = 227)	Completed ( <i>n</i> = 2,161)
<i>Study phase, n (%)</i>	Phase 0, 1, 1/2	82 (36)	1,625 (75)
	Phase 2, 2/3	31 (14)	51 (2)
	Phase 3, 4	57 (25)	120 (6)
	Unknown / missing	57 (25)	365 (17)
<i>Allocation status, n (%)</i>	Randomized	172 (76)	1,955 (90)
	Non-randomized	21 (9)	94 (4)
	Unknown / missing	34 (15)	112 (5)
<i>Blinding, n (%)</i>	Open	141 (62)	1,751 (81)
	Single blind	24 (11)	114 (5)
	Double blind	62 (27)	252 (12)
	Unknown / missing	0 (0)	44 (2)
<i>Interventional group, n (%)</i>	Single group	55 (24)	151 (7)
	Parallel	98 (43)	249 (12)
	Cross-over	69 (30)	1,707 (79)
	Factorial	5 (2)	8 (<1)
	Unknown / missing	0 (0)	46 (2)
<i>Endpoint classification, n (%)</i>	Bioavailability	47 (21)	418 (19)
	Bioequivalence	108 (48)	1,270 (59)
	Efficacy	14 (6)	26 (1)
	Pharmacokinetics and/or pharmacodynamics	16 (7)	239 (11)
	Safety	14 (6)	64 (3)
	Safety / efficacy	18 (8)	20 (1)
	Unknown / missing	10 (4)	124 (6)
<i>Primary purpose, n (%)</i>	Treatment	125 (55)	911 (42)
	Basic science	28 (12)	317 (15)
	Prevention	20 (9)	61 (3)
	Diagnostic	17 (7)	20 (1)
	Health services research	3 (1)	16 (1)
	Supportive care	6 (3)	7 (<1)
	Screening	0 (0)	7 (<1)
	Missing	28 (12)	822 (38)
<i>Sex, n (%)</i>	Female only	21 (9)	113 (5)
	Male only	20 (9)	424 (20)
	Both	186 (82)	1,616 (75)
	Unknown / missing	0 (0)	8 (<1)



Characteristic	Category	Bioequivalence & Bioavailability Trials	
		Ongoing ( <i>n</i> = 227)	Completed ( <i>n</i> = 2,161)
<i>Age groups, n (%)</i>	Children only	17 (7)	30 (1)
	Children and adults	23 (10)	48 (2)
	Adults only	187 (82)	2,083 (96)
<i>Expected sample size, median (IQR)</i>		50 (24 – 104)	32 (24 – 48)

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