Compliance of French academic clinical trials with the Clinical Trial Facilitation and Coordination Group recommendations on contraception and pregnancy testing requirements.

Running title: Contraception and pregnancy testing in trials.

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Abstract

Background/Aims

The Clinical Trials Coordination and Facilitation Group has issued recommendations on contraception and pregnancy testing to help sponsors meet regulatory expectations and harmonize practices to limit embryofetal risks in clinical trials. Our objective was to assess the compliance of French academic clinical trials with these recommendations and to describe the mitigation measures required by sponsors in their trials.

Methods

A cross-sectional study was performed on the French academic drug trials authorized by the national competent authority between January 2015 and June 2018. We included trials which tested systemic administration of drugs, and enrolled men or women of childbearing potential.

Results

Data from 97 trials included were compiled. One third of the trials [23.8%-43.3%] complied with the Clinical Trial Facilitation and Coordination Group recommendations. No improvement over time or according to embryofetotoxic status or drug duration exposure was found. Contraception was required in 56.7% of trials and was more often required in case of potentially embryofetotoxic drugs (68.5% versus 41.9%, p = 0.013) or exposure over one month (71.7% versus 43.8%, p = 0.006). Pregnancy testing at inclusion was required in 59.1% of trials and additional testing in 17.2%. Pregnancy testing at inclusion was more often required in trials with drug exposure above one month (67.4% versus 45.8%, p = 0.035).

Conclusion

French academic sponsors barely met the recommendations on contraception and pregnancy testing potentially leading to embryofetal risks in case of pregnancy. They need to implement these recommendations quickly.

Keywords

Contraception, pregnancy testing, women of childbearing potential, clinical trials guidelines, mitigation risk measures

Introduction

The scientific and ethical importance of including women of childbearing potential is widely acknowledged and the recruitment of women has been dramatically improved.[1, 2] However, considering the potential fetal harm of certain investigational drugs and the prevalence of unintended pregnancy, sponsors and regulatory authorities have to mitigate the risks. [3] For the M3 and E8 guidelines from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, characterization and minimization of these risks go through reproductive toxicity studies and appropriate precautions to prevent pregnancy during trials such as pregnancy testing, contraception methods or inclusion only after a confirmed menstrual period.[4, 5] According to these guidelines, women of childbearing potential should use "highly effective contraception" in order to participate in a trial. For male subjects, potential hazards of drug exposure to their sexual partners or resulting progeny should also be considered and appropriate contraception provisions should be included.[5] According to the American College of Obstetricians and Gynecologists, these recommendations should be adapted to trial profile (drug, treatment duration, actual risk of pregnancy of an individual research participant) but also to inherent risk of contraception.[6] During the past five years, two working groups provided recommendations on contraception and pregnancy testing in clinical trials to help sponsors meet regulatory expectations, harmonize practices and minimize the burden on subjects. The first recommendations were released in 2014 by the Clinical Trial Facilitation and Coordination Group on contraception and pregnancy testing.[7] The second recommendations were released in 2018 by the Clinical Trials Transformation Initiative specifically on pregnancy testing.[8] The NIH, also released a guideline in 2017 similar to the Clinical Trial Facilitation and Coordination Group recommendations.[9] The fact that several recommendations have recently been proposed highlights the importance of this topic. Despite this, few studies have been conducted so far.

These studies show contraception and pregnancy testing requirements are not consistently addressed. [10-14]

To the best of our knowledge, no study assessed the compliance with the Clinical Trial Facilitation and Coordination Group recommendations. As members of the French academic clinical trials safety working group (REVISE: REflexion sur la VIgilance et la Sécurité des Essais), we investigated how French academic sponsors managed this important issue.

The aim of our study was first to assess the implementation of the Clinical Trial Facilitation and Coordination Group recommendations on contraception and pregnancy testing in French academic clinical trials and then to describe the sponsors requirements.

Material and methods

We performed a cross-sectional study on clinical trials conducted by French academic sponsors belonging to the French academic safety working group REVISE.

Trials were selected according to the following inclusion criteria: (a) systemic administration of drugs, (b) enrollment of men or women of childbearing potential and (c) authorized by the French competent authority, between January 2015 (6 months after the release of the Clinical Trial Facilitation and Coordination Group recommendations) and June 2018.

Pharmacokinetic/pharmacoeconomic studies or trials with patients already treated with investigational drugs at enrollment were not included.

Data collection

The data collected consisted of trial characteristics, investigational drugs, contraception and pregnancy testing measures and requirements from the French national competent authority

(Agence Nationale de Sécurité des Medicaments et des produits de santé, ANSM) or the ethics committee. Each sponsor collected data from the first version of the protocols they submitted for authorization to the national competent authority and the ethics committee. A standardized data extraction form was used. Data entry was centralized. In case of discrepancies or missing data, queries were returned to sponsors. Two specialists in drug issues in pregnancy independently determined, for each trial and each related investigational drug, the adapted contraception and pregnancy testing according to the Clinical Trial Facilitation and Coordination Group recommendations, regardless of drug exposure duration. [7] These recommendations contain different decision trees based on gender and non-clinical and clinical data on drugs. The trial was considered non-compliant with the recommendations if the contraception or the pregnancy testing measures required by the sponsor did not meet those from the Clinical Trial Facilitation and Coordination Group for the most at-risk investigation drug in the trial. Discrepancies were discussed between the two experts until they reached an agreement. Fetotoxic and teratogenic risks of drug were not individualized as no difference is made on this point in the recommendations. As drug exposure duration during pregnancy has a potential embryofetal impact, trials were categorized according to drug exposure duration: short exposure (one month or less) otherwise long exposure.

Data analysis

Continuous variables were presented with median [first quartile; third quartile] and categorical variables were presented as a percentage (and 95% confidence interval for the primary outcome). Comparisons were limited to avoid multiplicity. Comparisons were performed using χ^2, Fisher's exact test or Cochran-Armitage trend test for categorical variables and non-parametric tests for continuous variables (Mann–Whitney test, Kruskal–

Wallis test, or Wilcoxon-signed rank test). Analyses were performed on raw data, then according to drug embryofetotoxicity potential and exposure duration. Non-drug comparators were not included in the analysis. All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Inc., Cary, North Carolina). Differences were considered statistically significant when $p < 0.05$.

Results

Clinical trials characteristics

Thirteen French academic sponsors participated in this study and 97 trials were included according to the eligibility criteria (Figure 1). These trials were of various profiles (Table 1). All were single-state trials. The median number of trials per sponsor was 7 [5-10].

Investigational drugs characteristics

A total of 133 drugs based on the Anatomical therapeutic chemical classification (ATC) were identified (Table 2). Antineoplastic and immunomodulating agents were the most tested drugs (30.8%). Drug exposure lasted one day in 22 trials (22.7%) and one month or less in 48 trials (49.5%). In 54 trials (55.7%), patients were exposed to at least one potentially embryofetotoxic drug. Of the 78 potentially embryofetotoxic drugs, 37 were antineoplastic or immunomodulatory drugs. Of the 46 long-term exposure trials, 33 had potentially embryofetotoxic drugs versus 19 for the 48 short-term exposure trials.

Compliance with the Clinical Trial Facilitation and Coordination Group recommendations

One third of the trials (33.0%, [23.8-43.3]) complied with the Clinical Trial Facilitation and Coordination Group recommendations. The compliance did not differ with regard to potentially embryofetotoxic status, drug duration exposure or funding (10 of 28 trials for academics and pharmaceutical industry co-funding versus 22 of 69 trials for academics) (Table 3). Among the 24 trials without any requirements at inclusion, 9 tested potential embryofetotoxic drugs. Four sponsors did not meet the recommendations for their trials. No improvement was found throughout the study period (2015-2018) ($p = 0.41$).

Contraception and pregnancy testing requirements

Contraception (for men and women) was required in 56.7% of the 97 trials, pregnancy testing at inclusion in 59.1% and additional pregnancy testing in 17.2% of the 93 trials including women (Figure 1, Table 3). Of the 42 trials with no contraception requirement, 11 had no justification. For pregnancy test at inclusion, 17of the 54 trials requiring contraception for women did not have any requirement. Requirements of contraception in academic-funded trials were similar (39 of 69 trials) to that for trials co-funded by academics and pharmaceutical industry (16 of 28 trials). The result was similar for pregnancy testing at inclusion (36 of 69 trials versus 19 of 29 trials).

The percentage of trials with contraception requirements statistically differed with regard to potentially embryofetotoxic status and drug duration exposure. Similarly, pregnancy testing at inclusion was more often required in long-exposure trials but not for potentially embryofetotoxic drugs. During trials, no statistical differences were found for pregnancy testing during trials for embryofetotoxic status or drug exposure duration.

No improvement was found throughout the study period (2015-2018) regarding requirements for contraception at inclusion ($p = 0.55$) or pregnancy testing at inclusion ($p = 0.57$).

Pregnancy management

Management was stated in 17.5% of the protocols with better results in trials with potentially embryofetotoxic drugs (12 of 54 trials versus 5 of 43 trials) or long-exposure trials (13 of 46 trials versus 3 of 48 trials).

National competent authority or ethics committee

The national competent authority or ethics committee required additional information or risk mitigation measures related to contraception or pregnancy testing for 19 trials before they are considered approvable. The main issue was related to contraception for 8 of them. Requirements were significantly less frequent for short-exposure trials, but no statistical difference was observed for embryofetotoxic status (Table 3).

Discussion

To our knowledge, this is the first study to assess the compliance of clinical trials (academic or not) with the Clinical Trial Facilitation and Coordination Group recommendations on contraception and pregnancy testing. We found only 33.0% of the French academic clinical trials did comply with the recommendations during clinical trial application, potentially leading to embryofetal exposure to harmful drugs during trials. Nevertheless, this result must be moderated, as before obtaining authorization of the trial, sponsors must take into account the requirements from the competent national authorities or ethics committees. Moreover, in 49.5% of the trials, drug exposure was one month or less so if the sponsor had duly justified

the absence of embryofetal risk if any, these trials would also have been considered as compliant. Indeed, contraception requirements may be disproportionate to the actual risks associated with drug and contraception. The national competent authority or the ethics committee had requirements for only 19.6% of the trials. One can also wonder, considering our results, why they did not make requirements on more clinical trials before authorizing them. Finally, taking into account the points mentioned above, we can assume that 60 to 70% of the trials would have been compliant after their authorization. It is a better result, but still insufficient since 55.7% of trials had at least one potentially embryofetotoxic drug. This must be improved to avoid the risk of exposure of a developing fetus to potentially harmful drugs. Very few studies have been performed on this topic and comparative data are scarce. Contraceptive measure requirements were comparable to published results (36.2% to 82.1%) [10-13] but our results were lower for pregnancy testing at inclusion compared to 89.7% to 100.0% for other studies.[10, 11, 13]

We showed that although compliance was generally low, some sponsors tended to adapt contraceptive requirements to the embryofetotoxic profile of the drugs. Results in other studies are disparate. In a study on Type-2 diabetes medications trials, category-C drug trials (evidence of fetal risks in animals) are less likely to require contraceptive measures than category B drug trials (no known human or animal fetal risks) (29.9% vs. 57.1%, OR = 0.32, p = 0.001).[12] In another study, contraception is not required in 9% of trials with embryofetotoxic drugs.[11]

Unintended pregnancies account for about half of all pregnancies worldwide.[3] In HIV drug trials, Sibeko et al. found a pregnancy incidence rate of 3.95 per 100 woman/year despite a high-contraceptive method provided onsite at no cost throughout the study.[15] In an HIV prevention trial, new contraceptive users have an increased risk of pregnancy compared to established users (adjusted hazard ratio = 1.66).[16] In North America, for example, clinical trial

participants have financial incentives to participate in studies so sponsors and researchers have a moral responsibility to exclude the risk of unintended pregnancy or provide a clear justification.

Drug exposure duration must be taken into account in embryofetal risk mitigation as the longer the exposure, the higher the risk of pregnancy. In our study, contraception and pregnancy testing requirements were significantly more frequent in long-exposure trials. Vieira et al. found contraception was required in 72% of long-exposure trials versus 29% of short-exposure trials.[13] However, unlike our results, regardless of the duration of exposure, pregnancy testing at inclusion is required in more than 90% of trials.[13] Recommendations of the Clinical Trials Facilitation and Coordination Group allow requirements to be adapted according to the exposure duration or special situations such as emergency situations, hospitalized patients, Etc., but this must be justified by the sponsor.

Lasarte et al. found the required contraception type is better stated in industry-sponsored trials than in academic-sponsored trials (76% versus 24% respectively).[11] They explain this by a different approach to patient safety and legal issues. However, Stewart et al. show variability in contraception practices and governance among industrial sponsors due to differences in definitions (women of childbearing potential or contraception for example) and company policies.[14] This could apply to academic sponsors too. No differences by funding source appeared in our study for contraception requirement and in the Phelan et al. study (37.4% for industrial trials versus 27.3% for investigator trials).[12]

Our study was potentially underpowered. Due to its design, we have probably underestimated the actual prevalence of compliant trials, as already discussed. However, if we had decided to assess the compliance on the version of protocols already authorized, in addition to sponsors, we would also have assessed the compliance of the competent authority and ethics committees.

The sponsors who participated in our study are part of the REVISE working group representing the majority of French academic sponsors. Our study was conducted with sponsors of all sizes and research topics. Thus, we are confident in the generalization of our results across French academic research. We cannot be sure our sample is representative of practices across European academic research however, these recommendations were developed by the Heads of Medicines Agencies to promote harmonization of processes across the national competent authorities and sponsors indicating it is an important issue for European clinical trials. Similar studies would be interesting to assess the implementation of these recommendations in other European countries but also in national competent authorities.

Conclusion

Minimizing the risk of an unintended embryofetal exposure to a potentially harmful drug is a major concern in clinical research and regulatory communities. There is a real need for standardization of practices and sensitization of investigators and sponsors to this topic but also national competent authorities and ethics committees. The Clinical Trial Facilitation and Coordination Group recommendations can help with it. It has a risk-based approach that reconciles sensitive requirements to actual fetal risk assessments and is respectful of women's interests by including, for example, sexual activity and orientation of participants. It should be implemented worldwide.

Our results should encourage French academic sponsors and investigators to implement the recommendations. The different steps could be (a) a clear identification of embryofetal risks in protocols and consent documents; (b) adapted contraception requirements (type and duration) when necessary; (c) pregnancy testing requirements at inclusion and regularly, if appropriate. These actions could be done quickly by modifying sponsors trial templates and

standard operating procedures with the help of the French working group on safety in trials, REVISE.

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Author contribution

All authors carried out data extraction. SC planned the analyses. All authors approved the planned analyses. SC conducted all statistical analysis. ACB and SC assessed fetotoxic and teratogenic risks of investigational drugs. SC, POA, AC, MG, SD, SR, CR, TO, LPS interpreted the findings.

SC prepared the manuscript. All authors reviewed the final manuscript.

Declaration of Conflicting Interests

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The other authors declare that they have no conflict of interest.

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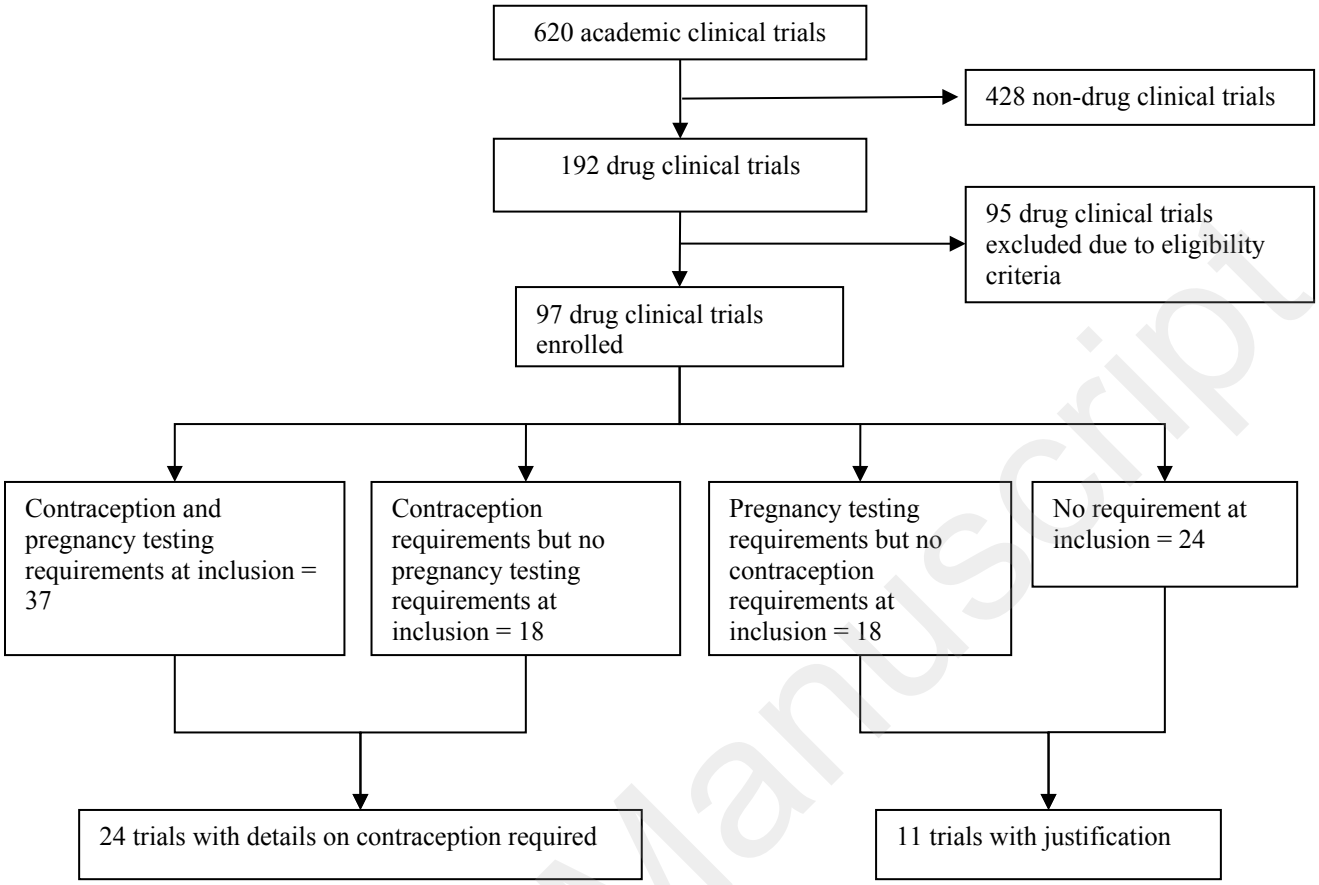

Figure 1. Flow of clinical trials according to the eligibility criteria.

Table 1. Characteristics of the 97 clinical trials included.

Characteristics of clinical trials	n (%)
Year of authorization from French Competent Authority	
2015	39 (40.2)
2016	32 (33.0)
2017	23 (23.7)
2018 (first semester)	3 (3.1)
Arms*	
1 arm	27 (27.8)
2 arms	63 (64.9)
3 and more arms	6 (7.2)
Population	
adults	90 (92.8)
children	5 (5.2)
both	2 (2.0)
Gender of participants	
male and female of childbearing potential	92 (94.8)
male only	4 (4.1)
female of childbearing potential only	1 (1.0)
Funding source	
public funding	69 (71.1)
public and industry funding	28 (28.9)
Phase[a]	
I	9 (9.3)
II	27 (27.8)
III	33 (34.0)
IV	27 (27.8)
Medical area	
Neurology/Psychiatry	17 (17.5)
Blood disorders/oncology	15 (15.5)
Cardiovascular diseases	12 (12.4)
Emergency care/Anesthetics/Pain	10 (10.3)
Infectious diseases	7 (7.2)
Endocrine disorders/Nutrition	5 (5.2)
Nephrology/Urology	5 (5.2)
Respiratory Medicine	5 (5.2)
Ear Nose Throat/Ophthalmology/Dentistry	4 (4.1)
Musculoskeletal disorders/Orthopedics	4 (4.1)
Dermatology	3 (3.1)
Gastroenterology/Hepatology	3 (3.1)
Pediatrics	2 (2.1)
Other	5 (5.2)

[a] There was missing data.

Table 2. Characteristics of investigational drugs.

	n (%)
Anatomical Therapeutic Chemical (ATC) Level (N=133)[a]	
A-Alimentary tract and metabolism	8 (6.0)
B-Blood and blood forming organs	16 (12.0)
C-Cardiovascular system	10 (7.5)
G-Genito-urinary system and sex hormones	1 (0.8)
H-Systemic hormonal preparations, excluding sex hormones and insulins	5 (3.7)
J-Anti-infectives for systemic use	11 (8.3)
L-Antineoplastic and immunomodulating agents	41 (30.8)
M-Musculo-skeletal system	6 (4.5)
N-Nervous system	14 (10.5)
P-Antiparasitic products, insecticides and repellents	1 (0.8)
R-Respiratory system	7 (5.3)
V-Various	9 (6.8)
No existing ATC	4 (3.0)
Potential embryofetotoxic drugs according to sponsors (N=140)[a]	78 (55.7)
Total duration of treatment (N=139)[a]	
≤ 1 day	27 (19.4)
]1 day; 1 week]	13 (9.4)
]1 week; 1 month]	22 (15.8)
]1 month; 3 months]	15 (10.8)
]3 months; 6 months]	22 (15.8)
>6 months	40 (28.8)

[a] some investigational drugs were found several times according to characteristics described;

Table 3. Contraception and pregnancy testing requirements in the clinical trials included.

	Total	Embryofetotoxicity		Exposure duration	
		No potential embryofetotoxic drug[b,]	At least one potential embryofetotoxic drug	Drug exposure ≤ one month	Drug exposure > one month
	% (n/N)	% (n/N)	% (n/N) p[c]	% (n/N)	% (n/N) p[c]
CTFG[a] conformity	33.0 [23.8-43.3][d] (32/97)	30.2 [17.2-46.1][d] (13/43)	35.2 [22.7-49.4][d] (19/54) p=0.61	25.0 [13.6-39.6][d] (12/48)	39.1 [25.1-54.6][d] (18/46) p=0.14
Contraception required at inclusion[c]	56.7 (55/97)	41.9 (18/43)	68.5 (37/54) p=0.013	43.8 (21/48)	71.7 (33/46) p=0.0061
Justification in case of no contraception requirements	26.2 (11/42)	28.0 (7/25)	23.5 (4/17)	25.9 (7/27)	30.8 (4/13)
Contraception required at inclusion for women of childbearing potential	58.1 (54/93)	43.9 (18/41)	69.2 (36/52) p=0.02	45.7 (21/46)	72.7 (32/44) p=0.009
Contraception required at inclusion for man	18.8 (18/96)	14.0 (6/43)	22.6 (12/53) p=0.31	6.3 (3/48)	31.1 (14/45) p=0.019
Contraception required at inclusion for female partner	8.3 (8/96)	9.3 (4/43)	7.6 (4/53) p=1.00	2.1 (1/48)	15.6 (7/45) p=0.027
Contraception required at inclusion for male partner	5.4 (5/93)	4.9 (2/41)	5.8 (3/52) p=1.00	4.4 (2/46)	6.8 (3/44) p=0.67
Women of childbearing potential defined in the protocol when a contraception is required[f]	29.6 (16/54)	33.3 (6/18)	27.8 (10/36)	28.6 (6/21)	31.3 (10/32)
Category of contraception required for woman of childbearing potential					
highly effective contraceptive measures	18.5 (10/54)	16.7 (3/18)	19.7 (7/36)	9.5 (2/21)	25.0 (8/32)
acceptable contraceptive measures	68.5 (37/54)	77.8 (14/18)	63.9 (23/36)	85.7 (18/21)	59.4 (19/32)
no detail provided	13.0 (7/54)	5.6 (1/18)	16.7 (6/36)	4.8 (1/21)	15.6 (5/32]
Contraception methods required–detailed	43.6 (24/55)	55.6 (10/18)	37.8 (14/37) p=0.22	52.4 (11/21)	39.4 (13/33) p=0.35
Contraception methods required					
combined hormonal	38.2 (21/55)	50.0 (9/18)	32.4 (12/37)	52.4 (11/21)	30.3 (10/33)

contraception					
progestogen-only oral hormonal contraception	30.9 (17/55)	38.9 (7/18)	27.0 (10/37)	38.1 (8/21)	27.3 (9/33)
intrauterine device	40.0 (22/55)	55.6 (10/18)	32.4 (12/37)	52.4 (11/21)	33.3 (11/33)
bilateral tubal occlusion	16.4 (9/55)	16.7 (3/18)	16.2 (6/37)	14.3 (3/21)	18.2 (6/33)
vasectomized partner	10.9 (6/55)	16.7 (3/18)	8.1 (3/37)	9.5 (2/21)	12.1 (4/33)
sexual abstinence	7.3 (4/55)	11.1 (2/18)	5.4 (2/37)	4.8 (1/21)	9.1 (3/33)
cap, diaphragm or sponge with spermicide	12.7 (7/55)	11.1 (2/18)	13.5 (5/37)	4.8 (1/21)	18.2 (6/33)
male or female condom	21.8 (12/55)	22.2 (4/18)	21.6 (8/37)	14.3(3/21)	27.3 (9/33)
other	10.9 (6/55)	5.6 (1/18)	13.5 (5/37)	9.5 (2/21)	12.1 (4/33)
Duration of use of contraception stated in protocols[a]	65.5 (36/55)	55.6 (10/18)	70.3 (26/37) p=0.28	52.4 (11/21)	72.7 (24/33) p=0.13
Pregnancy testing at inclusion	59.1 (55/93)	48.8 (20/41)	67.3 (35/52) p=0.07	45.8 (12/48)	67.4 (31/46) p=0.035
Additional pregnancy testing	17.2 (16/93)	14.6 (6/41)	19.2 (10/52) p=0.56	10.4 (5/48)	23.9 (11/46) p=0.08*
Contraception requirement form for women childbearing potential	31.5 (17/54)	38.9 (7/18)	27.8 (10/36)	38.1 (8/21)	28.1 (9/32)
Contraception requirement form for male	11.1 (6/54)	11.1 (2/18)	11.1 (4/36)	4.8 (1/21)	15.6 (5/32)
Contraception requirement form for partner	3.6 (2/55)	0.0 (0/18)	5.4 (2/37)	4.8 (1/21)	3.0 (1/33)
Grounds for non-acceptance from CA or EC requirements	19.6 (19/97)	18.6 (8/43)	20.4 (11/54) p=0.83	8.3 (4/48)	32.6 (15/46) p=0.0034

[a] CTFG = Clinical Trials Facilitation and coordination Group.
[b] There was missing data.
[c] Chi2 test or Fisher test, trials with at least one potential embryofetotoxic drug versus trials with no potential embryofetotoxic drugs and trials with drug exposure ≤ one month versus trials with drug exposure > one month.
[d] 95% confidence interval.