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Recruitment failure in Obstetrical & Gynaecological randomised controlled trials: a conundrum

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Recruitment failure in Obstetrical & Gynaecological randomised controlled trials: a conundrum

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ABSTRACT

Objective: We aim to assess which variables are associated with recruitment failure of Obstetrical & Gynaecological RCTs, leading to an extension of the study period.

Design: Nationwide study.

Setting: A cohort of RCTs supported by the trial centre of the Dutch Consortium of Obstetrics and Gynaecology.

Population: We included 83 RCTs that recruited patients between March 1st 2003 and December 1st 2023.

Main outcome measures: Main outcome was recruitment target not achieved within six months after the pre-planned recruitment period. Secondary outcomes were recruitment target not achieved within an extension period of at least twelve months and premature termination of the trial. In all RCTs, we collected information on variables with a potential effect on recruitment failure, recorded at five levels; patient, doctor, participating centre, study organisation and study design

Results: In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (where treatment is standard clinical practice), a compensation fee of less than 200 euros per included patient, funding of less than 350.000 euros, while a preceding pilot study lowered this risk.

Conclusions: We identified that the presence of a no-treatment arm, low funding and a low compensation fee per included patient were the most relevant risk factors for recruitment failure within the pre-planned period, while a preceding pilot study lowered this risk. Awareness of these variables is important when designing future studies.

Funding: Centre for Reproductive Medicine, Amsterdam University Medical Centres.

Key words: recruitment, randomised controlled trials, obstetrics, gynaecology

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Introduction

Randomised controlled trials (RCTs) are considered to be the best strategy in evaluating the effectiveness of medical interventions and they maintain a dominant position in the hierarchy of medical evidence(1). RCT outcomes are most often adopted into (inter) national clinical guidelines and have great influence on daily routine clinical practice. Unfortunately, obtaining evidence from RCTs is often hampered by failure to recruit enough patients within the pre-planned study period, leading to premature termination of the trial or extension of the study period(2).

Overall, a longer recruitment period may result in a shortage of resources possibly impacting the quality of the trial, limit the institutional capacity to start new RCTs, result in a trial that tries to answer a question that is no longer relevant, or result in premature termination of the study, thus hindering a conclusion with sufficient statistical power(3).

Premature termination due to poor recruitment has been estimated to occur in 9-10% of all RCTs(4-6). Variables that have been associated with these kind of poor recruitment are an overestimation of the number of eligible patients, a preference for one of the interventions by the patients, a high burden of the tested intervention for the patients, an unclear trial design, strict eligibility criteria, a lack of logistic support or a lack of funding(7-10).

While the variables that may result in poor recruitment leading to premature termination of the trial are known, much less is known on variables related to recruitment failure within the pre-planned study period, leading to extension of the study period.

The one study to investigate this matter, explored factors associated with recruitment in a cohort of 114 multicentre RCTs in more than nine clinical areas, including cancer, cardiology and obstetrics & gynaecology (18 RCTs had a clinical area classified as ‘other’), and funded by two public bodies in the United Kingdom; the UK Medical Research Council (MRC) and the Health Technology Assessment (HTA) Programme(6). RCTs that were funded by the MRC (as compared with the HTA) and were in the clinical area ‘cancer’, had better chances of good recruitment, which was a marginally statistically significant association. The vast heterogeneity of RCTs included in that study hampered the identification of other variables

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associated with poor recruitment and did not allow the authors to provide useful advice for improvement.

To assess factors that are associated with recruitment failure within the pre-planned study period, we performed a nationwide cohort study of RCTs within the homogeneous setting of the Dutch Consortium of Obstetrics & Gynaecology in the Netherlands. Such knowledge is crucial for researchers, trial centres and funding agencies to prevent this type of recruitment failure.

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Methods

Study design

This study was designed as a nationwide cohort study and included all multicentre RCTs carried out within the Dutch Consortium for Women's Health Research, embedded within the professional society, i.e. Dutch Society of Obstetrics and Gynaecology (NVOG)(11). The Dutch Consortium for Women's Health Research facilitated studies in obstetrics, gynaecology and reproductive medicine.

Within the consortium, participating clinical centres are both academic and non-academic hospitals. RCTs conducted within the Consortium are supported by a clinical trial centre (https://zorgevaluatienederland.nl/), a multidisciplinary trial bureau with methodologists, data managers, contract managers and trial managers. The trial centre staff supports research groups by advising on the budget, logistics, methods, and ethics approval, developing electronic case record forms, performing contract management and monitoring, creating the interim reports for the data safety and monitoring board and providing advice on the statistical analyses. The findings in our manuscript were reported according to the STROBE guideline(12).

Study population

We included finalized multicentre RCTs supported by the clinical trial centre and performed within the Dutch Consortium for Women's Health Research, between March 1st 2003 and December 1st 2023. We excluded studies with an observational design, single centre RCTs, RCTs initiated outside the Netherlands, RCTs with a cluster or parallel study design, RCTs that never actually started, RCTs in which inclusion of patients was still ongoing and RCTs prematurely discontinued for other reasons than poor recruitment, for example due to safety issues after an interim analysis.

Outcome measures

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Main outcome was recruitment target not achieved within 6 months after the pre-planned recruitment period. These RCTs were defined as RCTs with recruitment failure. The pre-planned recruitment period was documented by the principal investigator before the start of the trial. Secondary outcomes included recruitment target not achieved within an extension period of at least 12 months and premature termination of the trial (defined as stopping with including patients before the recruitment target was achieved). All studies that recruited during the COVID-19 pandemic received 6 months extension of their recruitment period.
In all RCTs, we collected information on variables with a potential effect on recruitment failure, identified after a scoping review. We recorded variables at five levels; patient, doctor, participating centre, study organisation and study design (Appendix 1).

Statistical analysis

For the primary outcome, we used the planned recruitment period as documented in the General Assessment and Registration form, a form that needs to be submitted to the ethical committee before actual start of the study. If we could not get access to this form, we retrieved this information from the main investigator and/or used the data mentioned in the protocol of the study. The actual recruitment period was calculated as the time between the first and last inclusion date.
We checked the continuous potential variables with spline curve analysis. We dichotomised on basis of the spline curve and used the median when the spline suggested a straight line.
We used logistic regression to evaluate the association between potential variables of recruitment failure and expressed these as odds ratios (OR) with corresponding 95% confidence intervals (CI).
To further explore the most relevant risk factors for recruitment failure multivariable risk prediction modelling was done by using both forward and backward stepwise logistic regression including all predictors at once (entry p=0.2 and exclusion p=0.1).
We used SPSS® (IBM 2019, USA) software for all statistical analyses (version 25).

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Ethics approval

Our study focussed on logistics and design issues and did not include patients as study participants. Consequently, we did not need ethical approval for this study.

Transparency statement

All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication. The manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

Role of the funding source

This study was supported by a small departmental grant of the Centre for Reproductive Medicine, Amsterdam University Medical Centres, location AMC.

Public and patient involvement

No patients or members of the public were involved in this study since the study did not concern patients directly.

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Results

Between March 1st 2003 and December 1st 2023 189 studies started recruitment and were assessed for eligibility. Of these, 106 studies did not fulfil our inclusion criteria, such that in total 83 RCTs were included in the analyses (Figure 1). Characteristics of the included studies are summarized in Table 1. Fifteen RCTs did not have funding at all (18%). A more detailed list of all RCTs can be found as supplementary file Appendix 2(13-89).

Primary and secondary outcomes

In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months (Table 2). Recruitment was not achieved within the pre-planned study period with a maximal extension period of 12 months in 41 RCTs (49%). Of these 41 RCTs, 29 studies had a total recruitment period of up to five years, and 12 RCTs finished their recruitment within five to ten years.

Nineteen RCTs (23%) stopped prematurely due to recruitment issues. Of these 19 RCTs, four studies reached 0 to 10% of their recruitment target, six studies 10 to 20%, two studies 20 to 30%, five studies 30 to 60% and two studies reached 70 to 80% of their planned recruitment target.

The mean recruitment period was 50 months (range 12-96 months) for RCTs with recruitment failure versus 31 months (range 12-91 months) for RCTs without recruitment failure. Twenty-two RCTs had a recruitment period of over 48 months. The actual absolute recruitment rate was 4.5 inclusions per month in RCTs with recruitment failure compared to 18.5 inclusions per month in RCTs without recruitment failure ($p<0.001$).

Potential variables of recruitment failure

The association of the potential variables with RCTs with recruitment failure i.e. RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 6 months, is shown in Table 3.

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Variables associated with higher chances on recruitment failure were presence of a no-treatment arm, having a design with more than two arms, funding, a compensation fee of less than 200 euros per included patient, funding of less than 350.000 euros and having more than four inclusion criteria. One variable associated with lower chances on recruitment failure was a preceding pilot study. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (OR 4.95, 95% CI 1.18 to 20.80), a compensation fee of less than 200 euros per included patient (OR 2.90, 95% CI 1.02 to 8.25)), funding of less than 350.000 euros (OR 2.99, 95% CI 1.05 to 8.51), while a preceding pilot study lowered the risk for treatment failure (OR 0.21, 95% CI 0.05 to 0.83).

When we compared the 41 RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 12 months, with the 42 RCTs that completed recruitment within that period, the described associations with treatment failure remained comparable in direction and size.

The most relevant variables for stopping prematurely were the absence of a preceding pilot study and having a no-treatment arm. None of the 19 RCTs that stopped prematurely had performed a pilot study (0%), compared to 17 of the 62 RCTs that completed recruitment (27%). Ten of the 19 RCTs that stopped prematurely had a no-treatment arm (52%), compared to eight of the 64 RCTs that completed recruitment (12.5%) (OR 6.13, 95% CI 1.98 to 19.06).

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Discussion

Main findings

In this nationwide cohort study, 46 of 83 included RCTs (55%) did not achieve their recruitment target within the pre-planned study period with a maximal extension period of six months. RCTs that had a no-treatment arm, low funding and low financial compensation per included patient were at risk to experience this type of recruitment failure, while a preceding pilot study lowered this risk. Upon extension of the pre-planned study period from six to twelve months, 41 RCTs (49%) still did not achieve the pre-planned recruitment target. Nineteen RCTs (23%) were stopped prematurely because of recruitment issues.

Strenghts and limitations

Our study has a number of strengths. First, we investigated recruitment failure in 83 RCTs embedded within the Dutch Consortium for Women's Health Research – and thus within one homogeneous discipline - with support and monitoring by the clinical trial centre. This allowed us to standardize several important aspects, like trial management and logistics, data collection and data monitoring. Second, we were able to assess all variables with a potential association with poor recruitment as described in literature; type of investigation, placebo-controlled study, treatment versus no treatment, whether the intervention was new or only available in the trial, whether the study was blinded or if there were any competing RCTs, number of study arms, number of inclusion and exclusion criteria, whether a pilot study was performed, number of participating centres and funding and compensation per included patient.

The main limitation of our study is the number of trials. Obviously, if we could have accessed an even larger cohort of trials, we might have been able to identify more potential variables for recruitment failure. A further limitation may be that within our study we focussed on objective variables, such as trial logistics and design issues. Other aspects, like patients' or practitioners' perspectives, which may affect recruitment as well were beyond the scope of our study.

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Interpretation

The design of a no-treatment arm where treatment is standard clinical practice was associated with recruitment failure. This design is particularly relevant, since we may be over-treating patients while we are actually in equipoise on whether the intervention is effective at all. Possibly, in this design specifically, the preference of the doctor or patient might play a role in the laborious recruitment. A no treatment arm was also associated with stopping prematurely, supporting its relevance as a risk factor. In our study ten (52%) of 19 RCTs that stopped prematurely had a no-treatment arm where in current clinical practice treatment is expected.

Two typical examples of RCTs with such a design that stopped prematurely were a trial that compared intrauterine insemination (IUI) with expectant management in couples with unexplained subfertility, and a trial that compared immediate delivery with temporizing management in women between 27+5 and 33+5 weeks of gestation admitted for early-onset severe preeclampsia with or without HELLP syndrome(33, 81).

Not very surprisingly, the lack of funding and compensation fee per included patient was associated with recruitment failure. Twelve studies with recruitment failure had no funding at all, compared with three studies without recruitment failure. In combination with our outcome that extending the recruitment period from six to twelve months did not increase the numbers of RCTs that reached their pre-planned sample size, this has important clinical, logistic and financial consequences. RCTs may reach their recruitment target, but in 12 RCTs in our study, recruitment took up to ten years. It implies that when recruitment is doomed to fail, it may reach its required sample size in the end, but at the expense of a lot of endurance and extra funding by a willing sponsor. On the other hand, RCTs can still be of extreme clinical importance if the research question is – and remains – relevant. This is shown by a trial that investigated low-molecular-weight heparin in women with recurrent pregnancy loss and inherited thrombophilia, which took 7,5 years to recruit, but results were eagerly awaited and eventually published in a high impact journal(15).

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A preceding pilot study lowers recruitment failure, while a study design with more than two arms or more than four inclusion criteria might increase the chance of recruitment failure, although with a wide confidence interval due to small numbers. We think that a preceding pilot study helps to notice and resolve potential issues before start of the actual study, while a study design with more than two arms or more than four inclusion criteria could result in an overly complex recruitment process. In a review of the literature on factors limiting the quality and progress of RCTs not hampered by recruitment failure, a straightforward study protocol and data collection as well as careful planning were also identified as key factors for completion(90).

A competing study was not associated with a lower chance on recruitment failure, which is the opposite of what we expected. We hypothesize that when more RCTs in the same field are recruiting patients at the same time, clinicians are more aware of the possibility of including patients in a particular RCT, or when one RCT recruits rapidly, this might be "contagious" for the other RCTs.

It is important to note that our results should not withhold clinicians from conducting RCTs on these research questions. Investigating the efficacy and safety of treatments and providing robust evidence can be of the utmost importance. Although it is known that the results of randomized and nonrandomized studies have a good correlation, nonrandomized studies tend to show larger treatment effects, and thus observational studies can be good adjunct to RCTs, but they cannot replace them(91, 92). More importantly, our study shows that also RCTs with recruitment that takes many years answer highly relevant clinical questions and can truly make a big difference in the clinical field. Principal investigators, sponsors and all who are participating in an RCT should be aware of the variables associated with poor recruitment, and that with dedication and persistence the RCT could be successfully completed and published.

Conclusion

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To conclude, RCTs with a no-treatment arm, low funding, low financial compensation per included patient are more likely to experience recruitment failure, while a preceding pilot study lowers this chance. We propose that investigators and grant providers consider these issues before the actual start of the study, to improve the chances of recruitment success. If a relevant trial is destined to have a suspected long recruitment period, it seems wise to ponder on the question whether to start the trial, or to accept a longer recruitment period with all its consequences.

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Disclosure of interest:

MG reports department research and educational grants from Guerbet and Ferring (location VUmc) outside the submitted work. BWM reports grants from NHMRC, personal fees from ObsEva, personal fees from Merck KGaA, personal fees from Guerbet, personal fees from iGenomix, outside the submitted work.

Contribution to Authorship:

JFWR, MvW, MCW and RGD conceived the study. JFWR and RC did the scope review, selected the potential variables, and collected the data. Differences of opinion and questions regarding the data were resolved with MvW. JFWR was responsible for the data. JFWR, RC and MvW analysed the data. JFWR, MvW, MG and FvdV drafted the manuscript, supported by BWM. All authors contributed to the critical revision of the paper and approved the final manuscript.

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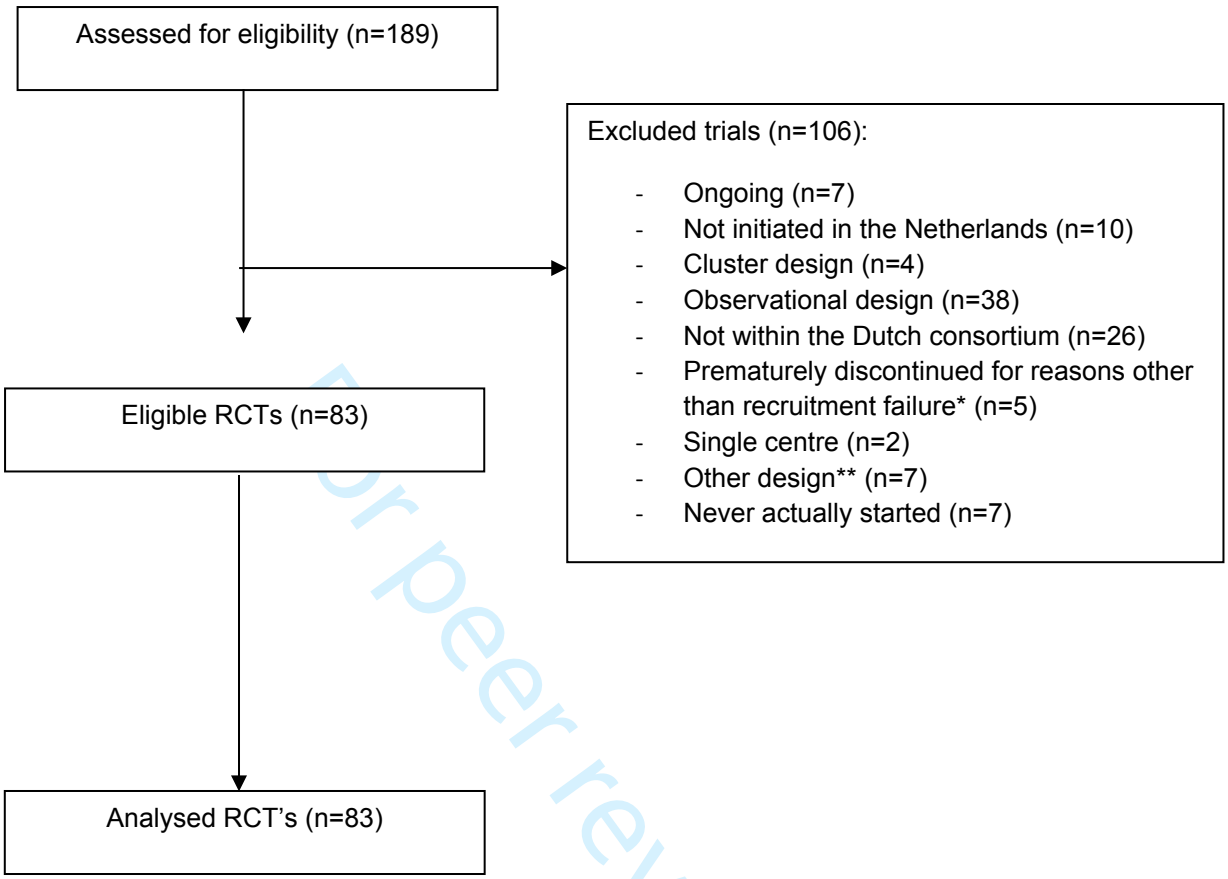
Figure 1. Flow diagram of studies



*In four studies on advice of the Data Safety Monitoring Board due to potential safety issues, and in one study because of revised insights based on new evidence.

**One study was a follow-up study of an RCT, three were implementation studies, one was a study to develop a decision tool, and one was a preference study.

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Table 1. Characteristics of the included studies

Characteristic	n (%)
Research area	
Obstetrics	32 (38)
Reproductive medicine	28 (34)
Oncology	5 (6)
(Uro)gynaecology	18 (22)
Tested intervention	
Drugs	20 (24)
Surgery	20 (24)
Infertility treatments	20 (24)
Obstetrical treatments	12 (15)
Gynaecological treatments	2 (2.4)
Diagnostic strategy	6 (7.2)
Tested intervention	
Existing intervention	69 (83)
New intervention	14 (17)
Tested intervention	
Only available in study	17 (20)
Available outside study	66 (80)
Blinding	18 (22)
No blinding	65 (78)
Number of arms	
2	77 (93)
>2	6 (7)
Pilot study	17 (20)
No pilot study	66 (80)
Recruiting centres	
Only Dutch centres	70 (84)
Including foreign centres	13 (16)
Funding	68 (82)
No funding	15 (18)

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Table 2. Recruitment details in the studies with recruitment failure and those with successful recruitment

	Recruitment failure (n= 46)		No recruitment failure (n=37)		p-value
Actual recruitment in months, mean (SD)	50	(20)	31	(12)	<0.001
0 - 12 months, n (%)	2	(5)	1	(3)	<0.001
12 - 24 months, n (%)	3	(5)	6	(16)	
2 - 3 years, n (%)	8	(18)	24	(69)	
3 - 4 years, n (%)	14	(29)	6	(13)	
> 4 years, n (%)	19	(45)	0	0	
Actual recruitment rate/month median (range)	4.5	(0.33 – 39)	18.5	(4 – 189)	<0.001

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Table 3. Association with potential variables

	Recruitment					
	Failure (n=46)		No failure (n=37)		OR (95% CI)	Adjusted OR (95% CI)*
Variables potentially associated with higher recruitment failure						
No treatment arm**	15	(33%)	3	(8%)	**5.48 (1.45 – 20.77)**	**4.95 (1.18 – 20.80)**
Arms > 2	5	(11%)	1	(3%)	4.39 (0.49 – 39.35)	
No funding vs funding	12	(26%)	3	(8%)	**4.00 (1.04- 15.45)**	
Compensation <€200	30	(65%)	12	(32%)	**3.91 (1.56 – 9.78)**	**2.90 (1.02 – 8.25)**
Funding <350.000	31	(67%)	13	(35%)	**3.82 (1.53 – 9.52)**	**2.99 (1.05 – 8.53)**
Inclusion criteria>4	17	(37%)	6	(16%)	**3.03 (1.05 -8.74)**	
Participating centres >25	17	(38%)	12	(32%)	1.27 (0.51 – 3.16)	
Surgical intervention	14	(30%)	9	(24%)	1.17 (0.72 -1.90)	
Variables potentially associated with lower recruitment failure						
Pilot study	4	(9%)	13	(35%)	**0.18 (0.05– 0.60)**	**0.21 (0.05– 0.83)**
New intervention	5	(11%)	9	(24%)	0.38 (0.12 – 1.25)	
Competing studies***	11	(24%)	13	(35%)	0.58 (0.22 – 1.51)	
Blinding	8	(17%)	10	(27%)	0.57 (0.20 – 1.63)	
Exclusion criteria <5	23	(50%)	23	(58%)	0.82 (0.32 – 2.09)	
Intervention available only in trial	9	(20%)	8	(22%)	0.88 (0.30 – 2.57)	

Data are in n (%)
*Applying both forward and backward step-wise logistic regression on all variables (entry p>0.2, exclusion p>0.1)
**In these randomised controlled trials (RCTs) no treatment was provided, when in daily practice, treatment was the standard
***During the recruitment phase of these RCTs, there was another RCT that recruited patients with the same inclusion criteria

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Appendix 1. List of variables recorded at five levels

Level	Variable
Patient	Were patients blinded or non-blinded
Doctor	Financial reimbursement for including patients
Participating centre	Setting (hospital, primary care, mixed)
Study organisation	Number of participating centres
	International versus national study
	Publication of results
	Funding
	Was the intervention new or existing (common practice)?
	Was the intervention only available in the study setting?
	Was there a competing study during the recruitment phase (including the same study population within the same timeframe)?
Study design	Was there a pilot study?
	Original and final sample size
	Subspecialisation
	Arms of the study
	Intervention type (surgery, medication, treatment)
	No treatment arm where treatment was the standard
	Placebo controlled
	Number of inclusion criteria
	Number of exclusion criteria

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Appendix 2. Detailed list of all included studies

Name study	Study population	Tested intervention	Comparison 1	Comparison 2	Publication	Funding in euros
Studies with recruitment failure						
Obstetrics						
APOSTEL-IV	Women with preterm pre-labour rupture without contractions of membranes 24-34 weeks	Drugs	Nifdipine	Placebo	Europ J of Obst & Gyn and Repr Biology 2016	0
APOSTEL VIII	Women with threatened preterm birth (gestational age 30-34 weeks)	Obstetrical treatments	Treatment with atosiban for 48 hours	Placebo	Not yet (analyzing data)	1,400,000
DIGITAT	Women with intra-uterine growth restriction beyond 36 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	BMJ 2010	400,000
GLUCOMOMS	Pregnant women with type 1 or 2 diabetes undergoing insulin therapy <16 or > 30 weeks	Obstetrical treatments	Intermittent use of retrospective continuous glucose monitoring	Standard treatment	Diabetes Obes metab 2018	300,000
HighLow	Pregnant women with a history of venous thromboembolism	Drugs	Weigh-adjusted intermediate-dose heparin	Fixed low-dose low-molecular-weight heparin	Lancet 2022	1,600,000
HYPITAT-II	Women with non-severe hypertensive disorders of pregnant 34-37 weeks gestation	Obstetrical treatments	Immediate delivery (induction of labour or caesarean section	Expectant management until 37 weeks of gestation	Lancet 2015	355,432
INDEX	Low risk women with an uncomplicated singleton pregnancy at 41 weeks	Obstetrical treatments	Induction of labour	Expectant management until 42 weeks	BMJ 2019	670,870
IUPC	Women in whom induced of augmented labour was required	Obstetrical treatments	Internal tocodynamometry	External monitoring	NEJM 2010	0

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PPROMEXIL-3	Women with a singleton pregnancy and preterm pre-labour rupture of the membranes 16-24 weeks gestation with oligohydramnios	Obstetrical treatments	Transabdominal amnion infusion	No intervention	Obstetrics & Gynaecology 2019	No funding
QP singletons	Women with a short cervix <35mm in a singleton and <38 mm in a multiple pregnancy	Obstetrical treatments	Cervical pessary	Progesterone	Submitted	No funding
SIMPLE-III	Term nulliparous women with a singleton pregnancy and a child in cephalic presentation and the Freidman partogram action line is crossed after regular interventions	Obstetrical treatments	Caesarean section	Expectant management, waiting until the simple partogram line is crossed	Unpublished	397,220
STOPORGO	Pregnant women gestational age <16 weeks who use SSRIs without clinically relevant depressive symptoms	Drugs	Preventive cognitive therapy with gradual guided discontinuation of SSRIs under medical management	Continue use of SSRIs	J Clin Psychiatry 2020	500,000
Sugardip	Women with GDM who do not reach target glycaemic control with modification of diet 16-34 weeks gestation	Drugs	Oral glucose lowering drugs	Insulin	Submitted	437,148
TOTEM	Women with severe preeclampsia, 28-34 weeks	Obstetrical treatments	Induction of labour	Expectant management	Acta Obstetrica et Gynecologica Scandinavica 2020	0
TRIPLE P	Women with a singleton pregnancy without a history of preterm birth and a cervix length ≤ 30 mm	Drugs	Progesterone	Placebo	Am J Perinatol 2015	1,000,000

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WOMB	Women with acute anaemia 12-24 hours postpartum without severe anaemic symptoms or comorbidities	Obstetrical treatments	Red blood cell transfusion	Expectant management	BJOG 2014	214,450
Reproductive medicine						
AID	Women who were eligible for donor sperm treatment with cryopreserved donor semen	Fertility treatments	Intracervical insemination with cryopreserved donor sperm	Intrauterine insemination	Human Reproduction 2021	276,000
ALIFE	Women with a history of unexplained recurrent pregnancy loss	Drugs	Aspirin*	Placebo	NEJM 2010	112,500
ALIFE2	Women with recurrent pregnancy loss and inherited thrombophilia	Drugs	Low-molecular-weight heparin + standard treatment	Standard treatment	Lancet 2023	1,200,000
COSY	Heterosexual couples diagnosed with (relatively) unexplained subfertility and a good prognosis	Fertility treatments	6 month web-based interactive educational programme of sex counselling	Expectant management	Submitted	300,000
DESH	Women aged 18-41 years with uni- or bilateral ultrasound visible hydrosalpinges who were scheduled for an IVF/ICSI treatment	Fertility treatment	Hysteroscopic proximal occlusion by intratubal device placement	Laparoscopic salpingectomy	Human Reproduction 2016	0
ESEP	Women with a laparoscopically confirmed tubal pregnancy and a healthy contralateral tube	Surgery	Salpingotomy	Salpingectomy	Lancet 2014	63,000
EX-IUI	Heterosexual couples with unexplained subfertility and a poor	Fertility treatments	6 months IUI with ovarian stimulation	6 months expectant management	Human Reproduction 2022	423,827

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	prognosis for natural conception					
FOAM	Infertile women who were scheduled for tubal patency testing during fertility work-up	Diagnostic strategies	Hysterosalpingo-foam sonography	Hysterosalpingography	Human Reproduction 2022	214,340
H2OLIE	Infertile women who were undergoing hysterosalpingography	Diagnostic strategies	Oil-based contrast	Water-based contrast	NEJM 2017	0
IVF38	Subfertile couples diagnosed with unexplained or mild male subfertility in which the women are 38-42 years old	Fertility treatments	IVF treatment	Expectant management	Manuscript in preparation	365,000
M-OVIN	Women with normogonadotropic anovulation not pregnant after six ovulatory cycles of clomiphene citrate	Drugs	Six cycles of gondadotrophines***	Six cycles of clomiphene citrate**	Lancet 2019	305,000
MASTER 1	Sub fertile couples with male subfertility, pre-wash total motile sperm count 3-10 x 10^6	Fertility treatments	IUI	Expectant management	Manuscript in preparation	388,208
MASTER 2	Sub fertile couples with male subfertility, pre-was total motile sperm count <3 x 10^6	Fertility treatments	ICSI	IVF	Manuscript in preparation	388,208
MEDIUM2	Sub fertile couples undergoing an IVF/ICSI treatment	Fertility treatments	Culture medium G5 to culture all oocytes and resulting embryos of each patient	Culture medium CSCM	Manuscript in preparation	0
MISOREST	Women who had primary misoprostol treatment for miscarriage with sonographic evidence of incomplete evacuation of	Obstetrical treatment	Curettage	Expectant management	Human Reproduction 2016	216,000

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	the uterus					
SCRATCH OFO	Women with unexplained infertility and a good prognosis for spontaneous conception	Fertility treatment	Endometrial scratching in the luteal phase of the natural cycle	Expectant management	Manuscript in preparation	349,732
SOMA	Premenopausal women with pain and an ovarian endometrioma	Surgery	Medication	Surgery	Not yet	393,000
STIM	Women 18-43 with breast cancer who opted for banking of oocytes or embryos	Drugs	Ovarian stimulation**** plus tamoxifen	Standard ovarian stimulation	Human Reproduction 2022	300,000
T4life	Women who were TPO-Ab positive, 2 or more pregnancy losses and TSH normal range	Drugs	Levothyroxine	Placebo	Lancet Diabetes Endocrinol 2022	205,983
TRUST	Women with a septate uterus and a wish to conceive	Surgery	Uterine septum resection	Expectant management	Human Reproduction 2021	322,430
Oncology						
LAPOVCA	Patients with suspected advanced-stage ovarian cancer who qualified for primary cytoreductive surgery	Surgery	Laparoscopy	Primary cytoreductive surgery	J Clin Oncol 2016	322,430
PARIS	Women undergoing pelvic radiotherapy	Diagnostic strategies	Chondrotoin sulphate solution	Placebo	Unpublished	3,000
SOCCER	Women with recurrent platinum-sensitive epithelial ovarian cancer	Surgery	Secondary cytoreductive surgery + chemotherapy	Chemotherapy alone	Unpublished	0
(Uro)gynaecology						
CUPIDO-II	Women with a prolapse and occult stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	International Urogynecology Journal 2016	24,000

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HYSNICHE	Women with postmenstrual spotting after a cesarean section and a niche with a residual myometrium of at least 3 mm during sonohysterography	Surgery	Hysteroscopic resection of the niche	Expectant management	BJOG 2017	250,000
PEOPLE	Treatment naïve women with pelvic organ prolapse who present with moderate to severe symptoms	Surgery	Pessary therapy	Vaginal pelvic organ prolapse surgery	JAMA 2022	387,000
POMPOEN	Women with postmenopausal bleeding, an endometrial thickness >4mm and benign result from endometrial sampling	Diagnostic	Further diagnostic workup by hysteroscopy (preceded by saline infusion sonography)	Expectant management	BJOG 2016	0
PROSECCO	Women with a maximum of 3 symptomatic type 0 or 1 submucosal fibroids with maximum 3,5cm diameter	Surgery	Hysteroscopic myomectomy procedural sedation and analgesia with propofol in outpatient setting	General anaesthesia A operating theatre	Submitted	337,747
SALTO	Women with a history of hysterectomy presenting with symptomatic vaginal vault prolapse with or without concomitant cystocele and rectocele who chose to undergo surgery	Surgery	Laparoscopic sacrocolpopexy	Open abdominal sacrocolpopexy	nt Urogynaecol J 2017	350,000
VUSIS-I	Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Diagnostic strategies	Stress urinary incontinence therapy based on history, clinical examination, pad test and 48h voiding diary	Therapy based on the same parameters AND urodynamic findings	Neurourol Urodyn 2012	151,000

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WOMAN	Women with a symptomatic cyst or abscess of the Bartholin gland	Gynaecological treatment	Treatment with Word catheter	Marsupialisation	BJOG 2016	0
Studies without recruitment failure						
Obstetrics						
2CLOSE	Caesarean section	Surgery	Single layer uterine closure	Double layer uterine closure	BJOG 2021	359,143
ALLO	Women in labour at term with clinical indices of foetal hypoxia prompting immediate delivery	Drugs	Allopurinol	Placebo	Arch Dis Child Fetal Neonatal Ed 2015	124,576
AMPHIA	Women with a multiple pregnancy	Drugs	Progesterone injections	Placebo	Obstetrics & Gynaecology 2011	400,000
APOSTEL-I	Women with symptoms of preterm labour 24-34 weeks, negative fibronectin test	Drugs	Nifedipine	Placebo	Am J Perinatol 2015	286,413
APOSTEL-II	Women with threatened preterm labour 26-32 weeks after tocolysis and corticosteroids 48 hours	Drugs	Nifedipine for 12 days	Placebo	JAMA 2013	316,168
APOSTEL-III	Women with threatened preterm birth 25-34 weeks	Drugs	Nifidipine	Atosiban	Lancet 2016	320,000
APRIL	Women with a singleton pregnancy and history of spontaneous preterm birth of singleton between 22 and 37 weeks	Drugs	Low dose aspirin	Placebo	PLOS Med 2022	351,898
HYPITAT	Women with a singleton pregnancy 36-41 weeks with gestational hypertension or mild pre-	Obstetrical treatments	Induction of labour	Expectant management	Lancet 2009	380,000

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	eclampsia					
MOTHER	Women with hyperemesis gravidarum	Obstetrical treatments	Enteral tube feeding	Standard care	Am J Clin Nutr 2017	1,000
PPROMEXIL	Non-labouring women with >24h preterm pre-labour rupture of membranes 34-37 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	PLos medicine 2012	600,000
PPROMEXIL-2	Non-labouring women with preterm pre-labour rupture of membranes	Obstetrical treatments	Induction of labour	Expectant management	Am J Obstet Gynaecol 2012	600,000
PROBAAT	Women with an unfavourable cervix	Obstetrical treatments	Foley catheter	Vaginal prostaglandin E2 gel	Lancet 2011	0
PROBAAT-II	Women with a term singleton pregnancy and an unfavourable cervix	Obstetrical treatments	Foley catheter	Misoprostol	Lancet 2016	80,000
PROTWIN	Women with a multiple pregnancy 12-20 weeks gestation	Obstetrical treatments	Cervical pessary	Control group	Lancet 2013	313,399
RAVEL	Women with an intermediate to high obstetric risk with an intention to deliver vaginally	Obstetrical treatment	Pain relief strategy with patient controlled remifentanil	Epidural analgesia	BMJ 2015	450,000
STAN	Labouring women with a high-risk singleton pregnancy in cephalic presentation beyond 36 weeks of gestation	Obstetrical treatments	Monitoring by cardiotocography with ST analysis	Cardiotocography only	Obstetrics & Gynaecology 2010	400,000
Reproductive medicine						
Antarctica2	Timing frozen embryo transfers	Fertility treatments	Home-based monitoring of ovulation	Hospital-controlled monitoring	Lancet 2023	599,375
BEDREST	Women having intrauterine insemination	Fertility treatments	15 minutes of immobilisation after insemination	Immediate immobilisation	BMJ 2009	0
INES	Couples seeking fertility	Fertility treatments	Three cycles of in	Six cycles of in vitro	BMJ 2015	374,116

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	treatment unexplained or mild male subfertility		vitro fertilisation with single embryo transfer	fertilisation in a modified natural cycle**		
INSIGHT	Women with a normal transvaginal ultrasound of the uterine cavity who were scheduled for their first IVF treatment	Surgery	Hysteroscopy with treatment of detected intra-cavity abnormalities before start IVF	Immediate start of IVF	Lancet 2016	474,147
LIFESTYLE	Infertile women with a BMI of 29 or higher who did not conceive naturally	Fertility treatments	6 month lifestyle-intervention program preceding 18 months of infertility treatment	Prompt infertility treatment	NEJM 2016	766,000
OPTIMIST	Women initiating IVF/ICSI	Drugs	Dose adjustment according to AFC	Standard dose	Human reproduction 2017	480,000
SCRATCH	Women with one previous failed IVF/ICSI treatment and planning a second fresh IVF/ICSI treatment	Surgery	Endometrium scratching	Standard treatment	Human reproduction 2021	550,899
SelecTimo	Couples undergoing in-vitro fertilisation or intracytoplasmic sperm injection	Fertility treatments	Time-lapse routine or early embryo viability assessment	Standard treatment	Lancet 2023	650,000
SUPER	Couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation	Drugs	FSH	Clomiphene citrate	Human Reproduction 2018	314,310
TOF	Women under 43 years receiving a IVF/ICSI treatment	Fertility treatments	Blastocyst stage (day 5) embryo transfer	Cleavage stage (day 3) embryo transfer	Submitted	700,000
Oncology						
TLH	Women with stage I endometrioid	Surgery	Total laparoscopic hysterectomy	Total abdominal hysterectomy	Lancet 2010	400,000

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	adenocarcinoma or complex atypical hyperplasia					
Vaccin	Adult female patients diagnosed with (histologically proven) CIN II-III and treated with LEEP and no prior vaccination for HPV	Drugs	HPV vaccination	Placebo	Awaiting follow-up	Unknown
(Uro)gynaecology						
CUPIDO-I	Women with a prolapse and evident stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	BJOG 2015	0
EVA	Postmenopausal women undergoing primary pelvic organ prolapse surgery POP-Q stage >2	Drugs	Vaginal oestrogen cream	Placebo	Manuscript in preparation	250,000
MIRA1	Women with heavy menstrual bleeding without intracavitary pathology	Gynaecological treatments	Levonorgestrel releasing intrauterine system (Mirena)	Bipolar radiofrequency endometrial ablation (Novasure)	Am J Obstet Gynecol 2021	409,270
MIRA2	Women with heavy menstrual bleeding who opt for treatment with endometrial ablation	Surgery	Endometrial ablation plus LNG-IUS	Endometrial ablation	Manuscript in preparation	473,852
PORTRET	Women with stress urinary incontinence	Surgery	Physiotherapy	Midurethral-sling surgery	NEJM 2013	400,000
SAM	Women with symptomatic POP in any stage, uterine descent and POP point D <minus 1 cm	Surgery	Sacrospinous hysteropexy	Modified Manchester surgery	JAMA 2023	489,891
SAVE U	Women with uterine prolapse stage 2 or higher requiring surgery and no history of pelvic floor surgery	Surgery	Sacrospinous hysteropexy	Vaginal hysterectomy with suspension of the uterosacral ligaments	BMJ 2015	Unknown

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VUSIS-II	Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Surgery/diagnostic strategy	Surgical therapy	Any other therapy (surgical therapy or conservative treatments) as based on individual findings	Neurourol Urodyn 2012	151,000

*with or without nadroparin **or six cycles of intrauterine insemination with ovarian hyper stimulation ***with intrauterine insemination or intercourse ****plus tamoxifen or letrozol

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Recruitment failure in Obstetrical & Gynaecological randomised controlled trials: a conundrum

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Recruitment Challenges in Obstetrical and Gynaecological Multi-Centre RCTs: A Nationwide Review (2003-2023)

AUTHORS

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ABSTRACT

Objective: We aim to assess which variables are associated with recruitment failure of obstetrical and gynaecological RCTs, leading to an extension of the study period.

Design: Nationwide study.

Setting: A cohort of RCTs supported by the trial centre of the Dutch Consortium of Obstetrics and Gynaecology.

Population: We included 83 RCTs that recruited patients between March 1st 2003 and December 1st 2023.

Main outcome measures: Main outcome was recruitment target not achieved within six months after the pre-planned recruitment period. Secondary outcomes were recruitment target not achieved within an extension period of at least twelve months and premature termination of the trial. In all RCTs, we collected information on variables with a potential effect on recruitment failure, recorded at five levels; patient, doctor, participating centre, study organisation and study design

Results: In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (where treatment is standard clinical practice), a compensation fee of less than 200 euros per included patient, funding of less than 350.000 euros, while a preceding pilot study lowered this risk.

Conclusions: We identified that the presence of a no-treatment arm, low funding and a low compensation fee per included patient were the most relevant risk factors for recruitment failure within the pre-planned period, while a preceding pilot study lowered this risk. Awareness of these variables is important when designing future studies.

Funding: Centre for Reproductive Medicine, Amsterdam University Medical Centres.

Key words: recruitment, randomised controlled trials, obstetrics, gynaecology

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Introduction

Randomised controlled trials (RCTs) are are widely regarded as the gold standard for assessing the effectiveness of medical interventions and hold a leading position in the hierarchy of medical evidence.[1]. RCT outcomes are most often adopted into (inter) national clinical guidelines and have great influence on daily routine clinical practice. Unfortunately, obtaining evidence from RCTs is often hampered by failure to recruit enough patients within the pre-planned study period, leading to premature termination of the trial or extension of the study period[2].

Overall, a longer recruitment period may result in a shortage of resources possibly impacting the quality of the trial, limit the institutional capacity to start new RCTs, can postpone the availability of beneficial interventions, permit harmful or ineffective interventions to remain in use for longer than ethically warranted, or result in premature termination of the study, thus hindering a conclusion with sufficient statistical power[3].

Premature termination due to poor recruitment has been estimated to occur in 9-10% of all RCTs[4-6]. Variables that have been associated with poor recruitment leading to premature termination are an overestimation of the number of eligible patients, a preference for one of the interventions by the patients, a high burden of the tested intervention for the patients, an unclear trial design, strict eligibility criteria, a lack of logistic support or a lack of funding[7-10]. While the variables that may result in poor recruitment leading to premature termination of the trial are known, much less is known on variables related to recruitment failure within the pre-planned study period, leading to extension of the study period.

The one study to investigate this matter, explored factors associated with recruitment in a cohort of 114 multicentre RCTs in more than nine clinical areas, including cancer, cardiology and obstetrics and gynaecology (18 RCTs had a clinical area classified as ‘other’), and funded by two public bodies in the United Kingdom; the UK Medical Research Council (MRC) and the Health Technology Assessment (HTA) Programme[6]. RCTs that were funded by the MRC (as compared with the HTA) and were in the clinical area ‘cancer’, had better chances of good recruitment, which was a marginally statistically significant association. The vast

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heterogeneity of RCTs included in that study hampered the identification of other variables associated with poor recruitment and did not allow the authors to provide useful advice for improvement.

To assess factors that are associated with recruitment failure within the pre-planned study period, we performed a nationwide cohort study of RCTs within the homogeneous setting of the Dutch Consortium of Obstetrics and Gynaecology in the Netherlands. Such knowledge is crucial for researchers, trial centres and funding agencies to prevent this type of recruitment failure.

Strengths and limitations of this study

- Recruitment failure was assessed in RCTs performed within a standardized setting with support and monitoring by the same clinical trial centre.
- We were able to assess all infrastructural variables with a potential association with poor recruitment as described in literature
- The study is limited by the number of trials
- The standardized setting may limit the generalisability as many RCTs are conducted in settings without such an infrastructure.
- Patients' or practitioners' perspectives, which may affect recruitment as well were beyond the scope of our study.

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Methods

Study design

This study was designed as a nationwide cohort study and included all multicentre RCTs carried out within the Dutch Consortium for Women's Health Research, embedded within the professional society, i.e. Dutch Society of Obstetrics and Gynaecology (NVOG)[11]. The Dutch Consortium for Women's Health Research facilitated studies in obstetrics, gynaecology and reproductive medicine.

Within the Consortium, participating clinical centres are both academic and non-academic hospitals. RCTs conducted within the Consortium are supported by a clinical trial centre (https://zorgevaluatienederland.nl/), a multidisciplinary trial bureau with methodologists, data managers, contract managers and trial managers. The trial centre staff supports research groups by advising on the budget, logistics, methods, and ethics approval, developing electronic case record forms, performing contract management and monitoring, creating the interim reports for the data safety and monitoring board and providing advice on the statistical analyses. The findings in our manuscript were reported according to the STROBE guideline[12].

Study population

We included finalized multicentre RCTs supported by the clinical trial centre and performed within the Dutch Consortium for Women's Health Research, between March 1st 2003 and December 1st 2023. We excluded studies with an observational design, single centre RCTs, RCTs initiated outside the Netherlands, RCTs with a cluster or parallel study design, RCTs that never actually started, RCTs in which inclusion of patients was still ongoing and RCTs prematurely discontinued for other reasons than poor recruitment, for example due to safety issues after an interim analysis.

Outcome measures

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Main outcome was recruitment target not achieved within 6 months after the pre-planned recruitment period. These RCTs were defined as RCTs with recruitment failure. The pre-planned recruitment period was documented by the principal investigator before the start of the trial. Secondary outcomes included recruitment target not achieved within an extension period of at least 12 months and premature termination of the trial (defined as stopping with including patients before the recruitment target was achieved). All studies that recruited during the COVID-19 pandemic received 6 months extension of their recruitment period.
In all RCTs, we collected information on variables with a potential effect on recruitment failure, identified after a scoping review. We recorded variables at five levels; patient, doctor, participating centre, study organisation and study design (Appendix 1).

Statistical analysis

For the primary outcome, we used the planned recruitment period as documented in the General Assessment and Registration form, a form that needs to be submitted to the ethical committee before actual start of the study. If we could not get access to this form, we retrieved this information from the main investigator and/or used the data mentioned in the protocol of the study. The actual recruitment period was calculated as the time between the first and last inclusion date.
We checked the continuous potential variables with spline curve analysis. We dichotomised on basis of the spline curve and used the median when the spline suggested a straight line.
We used logistic regression to evaluate the association between potential variables of recruitment failure and expressed these as odds ratios (OR) with corresponding 95% confidence intervals (CI).
To further explore the most relevant risk factors for recruitment failure multivariable risk prediction modelling was done by using both forward and backward stepwise logistic regression including all predictors at once (entry p=0.2 and exclusion p=0.1).
We used SPSS® (IBM 2019, USA) software for all statistical analyses (version 25).

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Ethics approval

Our study focussed on logistics and design issues and did not include patients as study participants. Consequently, we did not need ethical approval for this study.

Transparency statement

All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication. The manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

Role of the funding source

This study was supported by a small departmental grant from the Centre for Reproductive Medicine, Amsterdam University Medical Centres, location AMC.

Public and patient involvement

No patients or members of the public were involved in this study since the study did not concern patients directly.

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Results

Between March 1st 2003 and December 1st 2023 189 studies started recruitment and were assessed for eligibility. Of these, 106 studies did not fulfil our inclusion criteria, such that in total 83 RCTs were included in the analyses (Figure 1). Characteristics of the included studies are summarized in Table 1. Fifteen RCTs did not have funding at all (18%). A more detailed list of all RCTs can be found as supplementary file Appendix 2[13-89].

Primary and secondary outcomes

In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months (Table 2). Recruitment was not achieved within the pre-planned study period with a maximal extension period of 12 months in 41 RCTs (49%). Of these 41 RCTs, 29 studies had a total recruitment period of up to five years, and 12 RCTs finished their recruitment within five to ten years.

Nineteen RCTs (23%) stopped prematurely due to recruitment issues. Of these 19 RCTs, four studies reached 0 to 10% of their recruitment target, six studies 10 to 20%, two studies 20 to 30%, five studies 30 to 60% and two studies reached 70 to 80% of their planned recruitment target.

The mean recruitment period was 50 months (range 12-96 months) for RCTs with recruitment failure versus 31 months (range 12-91 months) for RCTs without recruitment failure. Twenty-two RCTs had a recruitment period of over 48 months. The actual absolute recruitment rate was 4.5 inclusions per month in RCTs with recruitment failure compared to 18.5 inclusions per month in RCTs without recruitment failure ($p<0.001$).

Potential variables of recruitment failure

The association of the potential variables with RCTs with recruitment failure i.e. RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 6 months, is shown in Table 3.

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Variables associated with higher chances on recruitment failure were presence of a no-treatment arm, having a design with more than two arms, a compensation fee of less than 200 euros per included patient, funding of less than 350 000 euros and having more than four inclusion criteria. One variable associated with lower chances on recruitment failure was a preceding pilot study. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (OR 4.95, 95% CI 1.18 to 20.80), a compensation fee of less than 200 euros per included patient (OR 2.90, 95% CI 1.02 to 8.25)), funding of less than 350 000 euros (OR 2.99, 95% CI 1.05 to 8.51), while a preceding pilot study lowered the risk for treatment failure (OR 0.21, 95% CI 0.05 to 0.83). When we compared the 41 RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 12 months, with the 42 RCTs that completed recruitment within that period, the described associations with treatment failure remained comparable in direction and size.

The most relevant variables for stopping prematurely were the absence of a preceding pilot study and having a no-treatment arm. None of the 19 RCTs that stopped prematurely had performed a pilot study (0%), compared to 17 of the 62 RCTs that completed recruitment (27%). Ten of the 19 RCTs that stopped prematurely had a no-treatment arm (52%), compared to eight of the 64 RCTs that completed recruitment (12.5%) (OR 6.13, 95% CI 1.98 to 19.06).

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Discussion

Main findings

In this nationwide cohort study, 46 of 83 included RCTs (55%) did not achieve their recruitment target within the pre-planned study period with a maximal extension period of six months. RCTs that had a no-treatment arm, low funding and low financial compensation per included patient were at risk to experience this type of recruitment failure, while a preceding pilot study lowered this risk. Upon extension of the pre-planned study period from six to twelve months, 41 RCTs (49%) still did not achieve the pre-planned recruitment target. Nineteen RCTs (23%) were stopped prematurely because of recruitment issues.

Strenghts and limitations

Our study has a number of strengths. First, we investigated recruitment failure in 83 RCTs embedded within the infrastructure of the Dutch Consortium for Women's Health Research – and thus within one homogeneous discipline – with support and monitoring by the clinical trial centre. This allowed us to standardize several important aspects, like trial management and logistics, data collection and data monitoring. Second, we were able to assess all variables with a potential association with poor recruitment as described in literature; type of investigation, placebo-controlled study, treatment versus no treatment, whether the intervention was new or only available in the trial, whether the study was blinded or if there were any competing RCTs, number of study arms, number of inclusion and exclusion criteria, whether a pilot study was performed, number of participating centres and funding and compensation per included patient.

The main limitation of our study is the number of trials. Obviously, if we could have accessed an even larger cohort of trials, we might have been able to identify more potential variables for recruitment failure. Furthermore, our study was done within a standardized setting which may limit the generalisability as many RCTs are conducted in settings without such an infrastructure. A further limitation may be that within our study we focussed on objective variables, such as trial logistics and design issues. Other aspects, like patients' or

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practitioners' perspectives, which may affect recruitment as well were beyond the scope of our study.

In our trials, when the target number was high, the prevalence was high as well. When writing up our protocol, it was decided that this should not be in input variable. We did an post-hoc analysis and found no impact of target number on failure.

Interpretation

The design of a no-treatment arm where treatment is standard clinical practice was associated with recruitment failure. This design is particularly relevant, since we may be over-treating patients while we are actually in equipoise on whether the intervention is effective at all. Possibly, in this design specifically, the preference of the doctor or patient might play a role in the laborious recruitment. A no treatment arm was also associated with stopping prematurely, supporting its relevance as a risk factor. In our study ten (52%) of 19 RCTs that stopped prematurely had a no-treatment arm where in current clinical practice treatment is expected.

Not very surprisingly, the lack of funding and compensation fee per included patient was associated with recruitment failure. Twelve studies with recruitment failure had no funding at all, compared with three studies without recruitment failure. Along with our finding that extending the recruitment period from six to twelve months did only slightly increase the number of RCTs achieving their pre-planned sample size, this has significant clinical, logistical, and financial implications.RCTs may reach their recruitment target, but in 12 RCTs in our study, recruitment took up to ten years. It implies that when recruitment is doomed to fail, it may reach its required sample size in the end, but at the expense of a lot of endurance and extra funding by a willing sponsor. On the other hand, RCTs can still be of extreme clinical importance if the research question is – and remains – relevant. This is shown by a trial that investigated low-molecular-weight heparin in women with recurrent pregnancy loss and inherited thrombophilia, which took 7,5 years to recruit, but results were eagerly awaited and eventually published in a high impact journal[15].

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A preceding pilot study lowers recruitment failure, while a study design with more than two arms or more than four inclusion criteria might increase the chance of recruitment failure, although with a wide confidence interval due to small numbers. We believe that conducting a preliminary pilot study can help identify and address potential challenges before the actual study begins. Our results furthermore suggest that a study design involving more than two arms or over four inclusion criteria may complicate the recruitment process excessively. In a review of the literature on factors limiting the quality and progress of RCTs not hampered by recruitment failure, a straightforward study protocol and data collection as well as careful planning were also identified as key factors for completion[90].

A competing study was not associated with a lower chance on recruitment failure, which is the opposite of what we expected. We hypothesize that when more RCTs in the same field are recruiting patients at the same time, clinicians are more aware of the possibility of including patients in a particular RCT, or when one RCT recruits rapidly, this might be "contagious" for the other RCTs.

It is important to note that our results should not withhold clinicians from conducting RCTs. Investigating the efficacy and safety of treatments and providing robust evidence can be of the utmost importance. Although it is known that the results of randomized and nonrandomized studies have a good correlation, nonrandomized studies tend to show larger treatment effects, and thus observational studies can be good adjunct to RCTs, but they cannot replace them[91, 92]. More importantly, our study shows that also RCTs with recruitment that takes many years may answer highly relevant clinical questions and can truly make a big difference in the clinical field. Principal investigators, sponsors and all who are participating in an RCT should be aware of the variables associated with poor recruitment, and that with dedication and persistence the RCT could be successfully completed and published.

Further research on how to improve recruitment efforts and increase the success of obstetrical and gynecological RCTs is needed. It would also be relevant to explore

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differences in infrastructure and funding rules and whether these influence recruitment success. Additionally, future research should investigate the perspectives of both patients and practitioners on why participants decline to join RCTs. This research could consider factors such as treatment preferences, as well as patients' fear, anxiety, mistrust in research, and challenges faced by low-income and non-English-speaking groups.

Conclusion

To conclude, RCTs with a no-treatment arm, low funding, low financial compensation per included patient are more likely to experience recruitment failure, while a preceding pilot study lowers this chance. We propose that investigators and grant providers consider these issues before the actual start of the study, to improve the chances of recruitment success. If a relevant trial is destined to have a suspected long recruitment period, it seems wise to ponder on the question whether to start the trial, or to accept a longer recruitment period with all its consequences.

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Contribution to Authorship:

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JFWR, MvW, MCW and RGD conceived the study. JFWR and RC did the scope review, selected the potential variables, and collected the data. Differences of opinion and questions regarding the data were resolved with MvW. JFWR was responsible for the data. JFWR, RC and MvW analysed the data. JFWR, MvW, MG and FvdV drafted the manuscript, supported by BWM. All authors contributed to the critical revision of the paper and approved the final manuscript. MvW and JR are responsible for the overall content as guarantor.

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Figure legends

Figure 1. Flow diagram of studies
Table 1. Characteristics of the included studies
Table 2. Recruitment details in the studies with recruitment failure and those with successful recruitment
Table 3. Association with potential variables
Appendix 1. List of variables recorded at five levels
Appendix 2. Detailed list of all included studies

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Table 1. Characteristics of the included studies

Characteristic	n (%)
Research area	
Obstetrics	32 (38)
Reproductive medicine	28 (34)
Oncology	5 (6)
(Uro)gynaecology	18 (22)
Tested intervention	
Drugs	20 (24)
Surgery	20 (24)
Infertility treatments	20 (24)
Obstetrical treatments	12 (15)
Gynaecological treatments	2 (2.4)
Diagnostic strategy	6 (7.2)
Tested intervention	
Existing intervention	69 (83)
New intervention	14 (17)
Tested intervention	
Only available in study	17 (20)
Available outside study	66 (80)
Blinding	18 (22)
No blinding	65 (78)
Number of arms	
2	77 (93)
>2	6 (7)
Pilot study	17 (20)
No pilot study	66 (80)
Recruiting centres	
Only Dutch centres	70 (84)
Including foreign centres	13 (16)
Funding	68 (82)
No funding	15 (18)

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Table 2. Recruitment details in the studies with recruitment failure and those with successful recruitment

	Recruitment failure (n= 46)		No recruitment failure (n=37)		p-value
Actual recruitment in months, mean (SD)	50	(20)	31	(12)	<0.001
0 - 12 months, n (%)	2	(5)	1	(3)	<0.001
12 - 24 months, n (%)	3	(5)	6	(16)	
2 - 3 years, n (%)	8	(18)	24	(69)	
3 - 4 years, n (%)	14	(29)	6	(13)	
> 4 years, n (%)	19	(45)	0	0	
Actual recruitment rate/month median (range)	4.5	(0.33 – 39)	18.5	(4 – 189)	<0.001

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Table 3. Association with potential variables

	Recruitment					
	Failure (n=46)		No failure (n=37)		OR (95% CI)	Adjusted OR (95% CI)*
Variables potentially associated with higher recruitment failure						
No treatment arm**	15	(33%)	3	(8%)	**5.48 (1.45 – 20.77)**	**4.95 (1.18 – 20.80)**
Arms > 2	5	(11%)	1	(3%)	4.39 (0.49 – 39.35)	
No funding vs funding	12	(26%)	3	(8%)	**4.00 (1.04 –15.45)**	
Compensation < €200	30	(65%)	12	(32%)	**3.91 (1.56 – 9.78)**	**2.90 (1.02 – 8.21)**
Funding < €350.000	31	(67%)	13	(35%)	**3.82 (1.53 – 9.52)**	**2.99 (1.05 – 8.52)**
Inclusion criteria > 4	17	(37%)	6	(16%)	**3.03 (1.05 – 8.74)**	
Participating centres > 25	17	(38%)	12	(32%)	1.27 (0.51 – 3.16)	
Surgical intervention	14	(30%)	9	(24%)	1.17 (0.72 – 1.90)	
Variables potentially associated with lower recruitment failure						
Pilot study	4	(9%)	13	(35%)	**0.18 (0.05 – 0.60)**	**0.21 (0.05 – 0.88)**
New intervention	5	(11%)	9	(24%)	0.38 (0.12 – 1.25)	
Competing studies***	11	(24%)	13	(35%)	0.58 (0.22 – 1.51)	
Blinding	8	(17%)	10	(27%)	0.57 (0.20 – 1.63)	
Exclusion criteria < 5	23	(50%)	23	(58%)	0.82 (0.32 – 2.09)	
Intervention available only in trial	9	(20%)	8	(22%)	0.88 (0.30 – 2.57)	

Data are in n (%)
*Applying both forward and backward step-wise logistic regression on all variables (entry p>0.2, exclusion p>0.1)
**In these randomised controlled trials (RCTs) no treatment was provided, when in daily practice, treatment was the standard
***During the recruitment phase of these RCTs, there was another RCT that recruited patients with the same inclusion criteria

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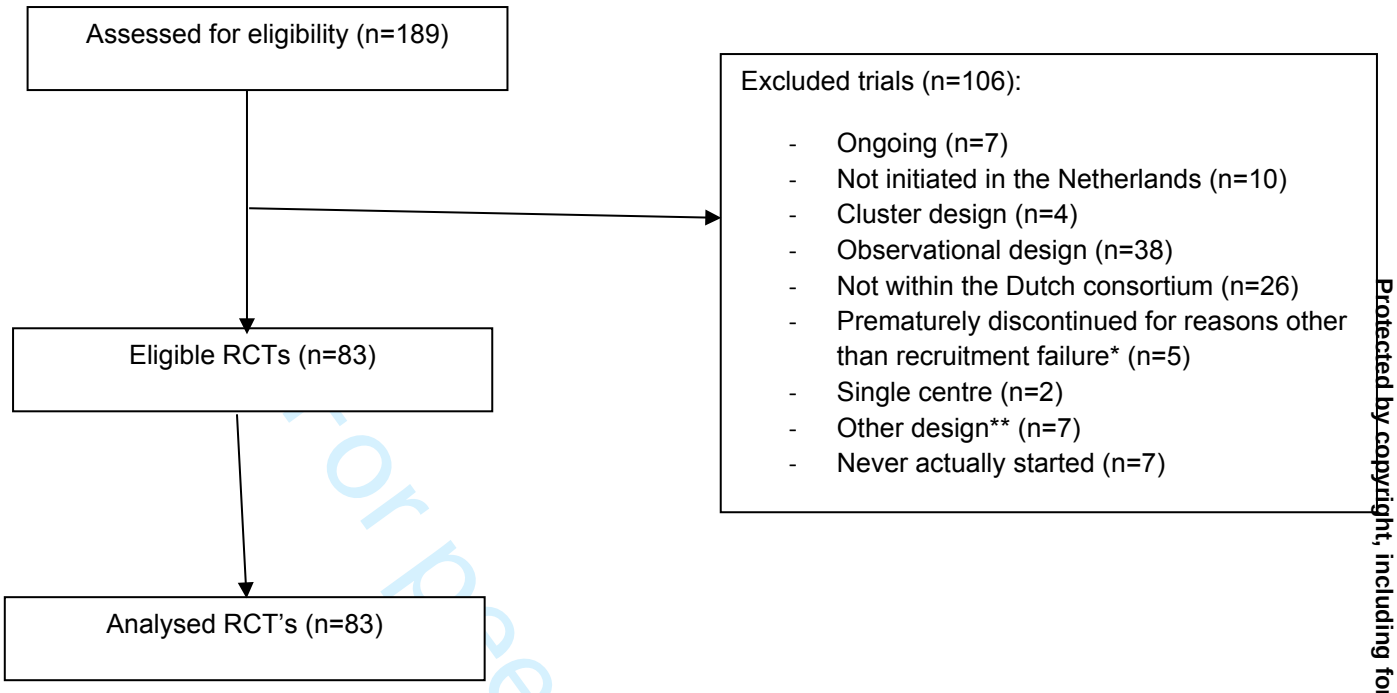
Figure 1. Flow diagram of studies



*In four studies on advice of the Data Safety Monitoring Board due to potential safety issues, and in one study because of revised insights based on new evidence.

**One study was a follow-up study of an RCT, three were implementation studies, one was a study to develop a decision tool, and one was a preference study.

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Appendix 1. List of variables recorded at five levels

Level	Variable
Patient	Were patients blinded or non-blinded
Doctor	Financial reimbursement for including patients
Participating centre	Setting (hospital, primary care, mixed)
Study organisation	Number of participating centres
	International versus national study
	Publication of results
	Funding
	Was the intervention new or existing (common practice)?
	Was the intervention only available in the study setting?
	Was there a competing study during the recruitment phase (including the same study population within the same timeframe)?
Study design	Was there a pilot study?
	Original and final sample size
	Subspecialisation
	Arms of the study
	Intervention type (surgery, medication, treatment)
	No treatment arm where treatment was the standard
	Placebo controlled
	Number of inclusion criteria
	Number of exclusion criteria

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Appendix 2. Detailed list of all included studies

Name study	Study population	Tested intervention	Comparison 1	Comparison 2	Publication	Funding in euros
Studies with recruitment failure						
Obstetrics						
APOSTEL-IV	Women with preterm pre-labour rupture of membranes without contractions 24-34 weeks	Drugs	Nifidipine	Placebo	Europ J of Obst & Gyn and Repr Biology 2016	0
APOSTEL VIII	Women with threatened preterm birth (gestational age 30-34 weeks)	Obstetrical treatments	Treatment with atosiban for 48 hours	Placebo	Not yet (analyzing data)	1,400,000
DIGITAT	Women with intra-uterine growth restriction beyond 36 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	BMJ 2010	400,000
GLUCOMOMS	Pregnant women with type 1 or 2 diabetes undergoing insulin therapy <16 or > 30 weeks	Obstetrical treatments	Intermittent use of retrospective continuous glucose monitoring	Standard treatment	Diabetes Obes metab 2018	300,000
HighLow	Pregnant women with a history of venous thromboembolism	Drugs	Weigh-adjusted intermediate-dose heparin	Fixed low-dose low-molecular-weight heparin	Lancet 2022	1,600,000
HYPITAT-II	Women with non-severe hypertensive disorders of pregnancy 34-37 weeks gestation	Obstetrical treatments	Immediate delivery (induction of labour or caesarean section)	Expectant management until 37 weeks of gestation	Lancet 2015	355,432
INDEX	Low risk women with an uncomplicated singleton pregnancy at 41 weeks	Obstetrical treatments	Induction of labour	Expectant management until 42 weeks	BMJ 2019	670,870
IUPC	Women in whom induced or augmented labour was required	Obstetrical treatments	Internal tocodynamometry	External monitoring	NEJM 2010	0

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PPROMEXIL-3	Women with a singleton pregnancy and preterm pre-labour rupture of the membranes 16-24 weeks gestation with oligohydramnios	Obstetrical treatments	Transabdominal amnion infusion	No intervention	Obstetrics & Gynaecology 2019	No funding
QP singletons	Women with a short cervix < 35mm in a singleton and < 38 mm in a multiple pregnancy	Obstetrical treatments	Cervical pessary	Progesterone	Submitted	No funding
SIMPLE-III	Term nulliparous women with a singleton pregnancy and a child in cephalic presentation and the Freidman partogram action line is crossed after regular interventions	Obstetrical treatments	Caesarean section	Expectant management, waiting until the simple partogram line is crossed	Unpublished	397,220
STOPORGO	Pregnant women gestational age < 16 weeks who use SSRIs without clinically relevant depressive symptoms	Drugs	Preventive cognitive therapy with gradual guided discontinuation of SSRIs under medical management	Continue use of SSRIs	J Clin Psychiatry 2020	500,000
Sugardip	Women with GDM who do not reach target glycaemic control with modification of diet 16-34 weeks gestation	Drugs	Oral glucose lowering drugs	Insulin	Submitted	437,148
TOTEM	Women with severe preeclampsia, 28-34 weeks	Obstetrical treatments	Induction of labour	Expectant management	Acta Obstetrica et Gynecologica Scandinavica 2020	0
TRIPLE P	Women with a singleton pregnancy without a history of preterm birth and a cervix length ≤ 30 mm	Drugs	Progesterone	Placebo	Am J Perinatol 2015	1,000,000

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WOMB	Women with acute anaemia 12-24 hours postpartum without severe anaemic symptoms or comorbidities	Obstetrical treatments	Red blood cell transfusion	Expectant management	BJOG 2014	214,450
Reproductive medicine						
AID	Women who were eligible for donor sperm treatment with cryopreserved donor semen	Fertility treatments	Intracervical insemination with cryopreserved donor sperm	Intrauterine insemination	Human Reproduction 2021	276,000
ALIFE	Women with a history of unexplained recurrent pregnancy loss	Drugs	Aspirin*	Placebo	NEJM 2010	112,500
ALIFE2	Women with recurrent pregnancy loss and inherited thrombophilia	Drugs	Low-molecular-weight heparin + standard treatment	Standard treatment	Lancet 2023	1,200,000
COSY	Heterosexual couples diagnosed with (relatively) unexplained subfertility and a good prognosis	Fertility treatments	6 month web-based interactive educational programme of sex counselling	Expectant management	Submitted	300,000
DESH	Women aged 18-41 years with uni- or bilateral ultrasound visible hydrosalpinges who were scheduled for an IVF/ICSI treatment	Fertility treatment	Hysteroscopic proximal occlusion by intratubal device placement	Laparoscopic salpingectomy	Human Reproduction 2016	0
ESEP	Women with a laparoscopically confirmed tubal pregnancy and a healthy contralateral tube	Surgery	Salpingotomy	Salpingectomy	Lancet 2014	63,000
EX-IUI	Heterosexual couples with unexplained subfertility and a poor	Fertility treatments	6 months IUI with ovarian stimulation	6 months expectant management	Human Reproduction 2022	423,827

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	prognosis for natural conception					
FOAM	Infertile women who were scheduled for tubal patency testing during fertility work-up	Diagnostic strategies	Hysterosalpingo-foam sonography	Hysterosalpingography	Human Reproduction 2022	214,340
H2OLIE	Infertile women who were undergoing hysterosalpingography	Diagnostic strategies	Oil-based contrast	Water-based contrast	NEJM 2017	0
IVF38	Subfertile couples diagnosed with unexplained or mild male subfertility in which the women are 38-42 years old	Fertility treatments	IVF treatment	Expectant management	Manuscript in preparation	365,000
M-OVIN	Women with normogonadotropic anovulation not pregnant after six ovulatory cycles of clomiphene citrate	Drugs	Six cycles of gondadotrophines***	Six cycles of clomiphene citrate**	Lancet 2019	305,000
MASTER 1	Subfertile couples with male subfertility, pre-wash total motile sperm count 3-10 x 10^6	Fertility treatments	IUI	Expectant management	Manuscript in preparation	388,208
MASTER 2	Subfertile couples with male subfertility, pre-was total motile sperm count < 3 x 10^6	Fertility treatments	ICSI	IVF	Manuscript in preparation	388,208
MEDIUM2	Subfertile couples undergoing an IVF/ICSI treatment	Fertility treatments	Culture medium G5 to culture all oocytes and resulting embryos of each patient	Culture medium CSCM	Manuscript in preparation	0
MISOREST	Women who had primary misoprostol treatment for miscarriage with sonographic evidence of incomplete evacuation of	Obstetrical treatment	Curettage	Expectant management	Human Reproduction 2016	216,000

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	the uterus					
SCRATCH OFO	Women with unexplained infertility and a good prognosis for spontaneous conception	Fertility treatment	Endometrial scratching in the luteal phase of the natural cycle	Expectant management	Manuscript in preparation	349,732
SOMA	Premenopausal women with pain and an ovarian endometrioma	Surgery	Medication	Surgery	Not yet	393,000
STIM	Women 18-43 years with breast cancer who opted for banking of oocytes or embryos	Drugs	Ovarian stimulation**** plus tamoxifen	Standard ovarian stimulation	Human Reproduction 2022	300,000
T4life	Women who were TPO-Ab positive, 2 or more pregnancy losses and TSH normal range	Drugs	Levothyroxine	Placebo	Lancet Diabetes Endocrinol 2022	205,983
TRUST	Women with a septate uterus and a wish to conceive	Surgery	Uterine septum resection	Expectant management	Human Reproduction 2021	322,430
Oncology						
LAPOVCA	Patients with suspected advanced-stage ovarian cancer who qualified for primary cytoreductive surgery	Surgery	Laparoscopy	Primary cytoreductive surgery	J Clin Oncol 2016	322,430
PARIS	Women undergoing pelvic radiotherapy	Diagnostic strategies	Chondrotoin sulphate solution	Placebo	Unpublished	3,000
SOCCER	Women with recurrent platinum-sensitive epithelial ovarian cancer	Surgery	Secondary cytoreductive surgery + chemotherapy	Chemotherapy alone	Unpublished	0
(Uro)gynaecology						
CUPIDO-II	Women with a prolapse and occult stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	International Urogynecology Journal 2016	24,000

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HYSNICHE	Women with postmenstrual spotting after a cesarean section and a niche with a residual myometrium of at least 3 mm during sonohysterography	Surgery	Hysteroscopic resection of the niche	Expectant management	BJOG 2017	250,000
PEOPLE	Treatment naïve women with pelvic organ prolapse who present with moderate to severe symptoms	Surgery	Pessary therapy	Vaginal pelvic organ prolapse surgery	JAMA 2022	387,000
POMPOEN	Women with postmenopausal bleeding, an endometrial thickness > 4 mm and benign result from endometrial sampling	Diagnostic	Further diagnostic workup by hysteroscopy (preceded by saline infusion sonography)	Expectant management	BJOG 2016	0
PROSECCO	Women with a maximum of 3 symptomatic type 0 or 1 submucosal fibroids with maximum 3.5 cm diameter	Surgery	Hysteroscopic myomectomy procedural sedation and analgesia with propofol in outpatient setting	General anaesthesia A operating theatre	Submitted	337,747
SALTO	Women with a history of hysterectomy presenting with symptomatic vaginal vault prolapse with or without concomitant cystocele and rectocele who chose to undergo surgery	Surgery	Laparoscopic sacrocolpopexy	Open abdominal sacrocolpopexy	nt Urogynaecol J 2017	350,000
VUSIS-I	Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Diagnostic strategies	Stress urinary incontinence therapy based on history, clinical examination, pad test and 48h voiding diary	Therapy based on the same parameters AND urodynamic findings	Neurourol Urodyn 2012	151,000

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WOMAN	Women with a symptomatic cyst or abscess of the Bartholin gland	Gynaecological treatment	Treatment with Word catheter	Marsupialisation	BJOG 2016	0
Studies without recruitment failure						
Obstetrics						
2CLOSE	Caesarean section	Surgery	Single layer uterine closure	Double layer uterine closure	BJOG 2021	359,143
ALLO	Women in labour at term with clinical indices of foetal hypoxia prompting immediate delivery	Drugs	Allopurinol	Placebo	Arch Dis Child Fetal Neonatal Ed 2015	124,576
AMPHIA	Women with a multiple pregnancy	Drugs	Progesterone injections	Placebo	Obstetrics & Gynaecology 2011	400,000
APOSTEL-I	Women with symptoms of preterm labour 24-34 weeks, negative fibronectin test	Drugs	Nifedipine	Placebo	Am J Perinatol 2015	286,413
APOSTEL-II	Women with threatened preterm labour 26-32 weeks after tocolysis and corticosteroids 48 hours	Drugs	Nifedipine for 12 days	Placebo	JAMA 2013	316,168
APOSTEL-III	Women with threatened preterm birth 25-34 weeks	Drugs	Nifidipine	Atosiban	Lancet 2016	320,000
APRIL	Women with a singleton pregnancy and history of spontaneous preterm birth of singleton between 22 and 37 weeks	Drugs	Low dose aspirin	Placebo	PLOS Med 2022	351,898
HYPITAT	Women with a singleton pregnancy 36-41 weeks with gestational hypertension or mild pre-	Obstetrical treatments	Induction of labour	Expectant management	Lancet 2009	380,000

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	eclampsia					
MOTHER	Women with hyperemesis gravidarum	Obstetrical treatments	Enteral tube feeding	Standard care	Am J Clin Nutr 2017	1,000
PPROMEXIL	Non-labouring women with > 24h preterm pre-labour rupture of membranes 34-37 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	PLos medicine 2012	600,000
PPROMEXIL-2	Non-labouring women with preterm pre-labour rupture of membranes	Obstetrical treatments	Induction of labour	Expectant management	Am J Obstet Gynaecol 2012	600,000
PROBAAT	Women with an unfavourable cervix	Obstetrical treatments	Foley catheter	Vaginal prostaglandin E2 gel	Lancet 2011	0
PROBAAT-II	Women with a term singleton pregnancy and an unfavourable cervix	Obstetrical treatments	Foley catheter	Misoprostol	Lancet 2016	80,000
PROTWIN	Women with a multiple pregnancy 12-20 weeks gestation	Obstetrical treatments	Cervical pessary	Control group	Lancet 2013	313,399
RAVEL	Women with an intermediate to high obstetric risk with an intention to deliver vaginally	Obstetrical treatment	Pain relief strategy with patient controlled remifentanil	Epidural analgesia	BMJ 2015	450,000
STAN	Labouring women with a high-risk singleton pregnancy in cephalic presentation beyond 36 weeks of gestation	Obstetrical treatments	Monitoring by cardiotocography with ST analysis	Cardiotocography only	Obstetrics & Gynaecology 2010	400,000
Reproductive medicine						
Antarctica2	Timing frozen embryo transfers	Fertility treatments	Home-based monitoring of ovulation	Hospital-controlled monitoring	Lancet 2023	599,375
BEDREST	Women having intrauterine insemination	Fertility treatments	15 minutes of immobilisation after insemination	Immediate immobilisation	BMJ 2009	0
INES	Couples seeking fertility	Fertility treatments	Three cycles of in	Six cycles of in vitro	BMJ 2015	374,116

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	treatment unexplained or mild male subfertility		vitro fertilisation with single embryo transfer	fertilisation in a modified natural cycle**		
INSIGHT	Women with a normal transvaginal ultrasound of the uterine cavity who were scheduled for their first IVF treatment	Surgery	Hysteroscopy with treatment of detected intra-cavity abnormalities before start IVF	Immediate start of IVF	Lancet 2016	474,147
LIFESTYLE	Infertile women with a BMI of 29 or higher who did not conceive naturally	Fertility treatments	6 month lifestyle-intervention program preceding 18 months of infertility treatment	Prompt infertility treatment	NEJM 2016	766,000
OPTIMIST	Women initiating IVF/ICSI	Drugs	Dose adjustment according to AFC	Standard dose	Human reproduction 2017	480,000
SCRATCH	Women with one previous failed IVF/ICSI treatment and planning a second fresh IVF/ICSI treatment	Surgery	Endometrium scratching	Standard treatment	Human reproduction 2021	550,899
SelecTimo	Couples undergoing in-vitro fertilisation or intracytoplasmic sperm injection	Fertility treatments	Time-lapse routine or early embryo viability assessment	Standard treatment	Lancet 2023	650,000
SUPER	Couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation	Drugs	FSH	Clomiphene citrate	Human Reproduction 2018	314,310
TOF	Women under 43 years receiving a IVF/ICSI treatment	Fertility treatments	Blastocyst stage (day 5) embryo transfer	Cleavage stage (day 3) embryo transfer	Submitted	700,000
Oncology						
TLH	Women with stage I endometrioid	Surgery	Total laparoscopic hysterectomy	Total abdominal hysterectomy	Lancet 2010	400,000

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	adenocarcinoma or complex atypical hyperplasia						
Vaccin	Adult female patients diagnosed with (histologically proven) CIN II-III and treated with LEEP and no prior vaccination for HPV	Drugs	HPV vaccination	Placebo	Awaiting follow-up	Unknown
(Uro)gynaecology						
CUPIDO-I	Women with a prolapse and evident stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	BJOG 2015	0
EVA	Postmenopausal women undergoing primary pelvic organ prolapse surgery POP-Q stage > 2	Drugs	Vaginal oestrogen cream	Placebo	Manuscript in preparation	250,000
MIRA1	Women with heavy menstrual bleeding without intracavitary pathology	Gynaecological treatments	Levonorgestrel releasing intrauterine system (Mirena)	Bipolar radiofrequency endometrial ablation (Novasure)	Am J Obstet Gynecol 2021	409,270
MIRA2	Women with heavy menstrual bleeding who opt for treatment with endometrial ablation	Surgery	Endometrial ablation plus LNG-IUS	Endometrial ablation	Manuscript in preparation	473,852
PORTRET	Women with stress urinary incontinence	Surgery	Physiotherapy	Midurethral-sling surgery	NEJM 2013	400,000
SAM	Women with symptomatic POP in any stage, uterine descent and POP point D < minus 1 cm	Surgery	Sacrospinous hysteropexy	Modified Manchester surgery	JAMA 2023	489,891
SAVE U	Women with uterine prolapse stage 2 or higher requiring surgery and no history of pelvic	Surgery	Sacrospinous hysteropexy	Vaginal hysterectomy with suspension of the uterosacral ligaments	BMJ 2015	Unknown

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VUSIS-II	floor surgery Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Surgery/diagnostic strategy	Surgical therapy	Any other therapy (surgical therapy or conservative treatments) as based on individual findings	Neurourol Urodyn 2012	151,000

*with or without nadroparin **or six cycles of intrauterine insemination with ovarian hyper stimulation ***with intrauterine insemination or intercourse ****plus tamoxifen or letrozol

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Which variables are associated with recruitment failure? A nationwide review in Obstetrical and Gynaecological Multi-Centre RCTs conducted in the Netherlands (2003-2023)

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Which variables are associated with recruitment failure? A nationwide review in Obstetrical and Gynaecological Multi-Centre RCTs (2003-2023)

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ABSTRACT

Objective: We aim to assess which variables are associated with recruitment failure of obstetrical and gynaecological RCTs, leading to an extension of the study period.

Design: Nationwide study.

Setting: A cohort of RCTs supported by the trial centre of the Dutch Consortium of Obstetrics and Gynaecology.

Population: We included 83 RCTs that recruited patients between March 1st 2003 and December 1st 2023.

Main outcome measures: Main outcome was recruitment target not achieved within six months after the pre-planned recruitment period. Secondary outcomes were recruitment target not achieved within an extension period of at least twelve months and premature termination of the trial. In all RCTs, we collected information on variables with a potential effect on recruitment failure, recorded at five levels; patient, doctor, participating centre, study organisation and study design.

Results: In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (where treatment is standard clinical practice), a compensation fee of less than 200 euros per included patient, funding of less than 350 000 euros, while a preceding pilot study lowered this risk.

Conclusions: We identified that the presence of a no-treatment arm, low funding and a low compensation fee per included patient were the most relevant risk factors for recruitment failure within the pre-planned period, while a preceding pilot study lowered this risk. Awareness of these variables is important when designing future studies.

Funding: Centre for Reproductive Medicine, Amsterdam University Medical Centres.

Key words: recruitment, randomised controlled trials, obstetrics, gynaecology

Strengths and limitations of this study

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- Recruitment failure was assessed in a nationwide collection of RCTs performed within a standardized setting with support and monitoring by the same clinical trial centre.
- This study was able to assess all infrastructural variables with a potential association with poor recruitment as described in literature.
- The study is limited by the number of trials.
- The standardized setting may limit the generalisability as many RCTs are conducted in settings without such an infrastructure.
- A limitation of the study was that it did not include patients' or practitioners' perspectives, which may affect recruitment as well were.

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Introduction

Randomised controlled trials (RCTs) are are widely regarded as the gold standard for assessing the effectiveness of medical interventions and hold a leading position in the hierarchy of medical evidence[1]. RCT outcomes are most often adopted into (inter) national clinical guidelines and have great influence on daily routine clinical practice. Unfortunately, obtaining evidence from RCTs is often hampered by failure to recruit enough patients within the pre-planned study period, leading to premature termination of the trial or extension of the study period[2].

Overall, a longer recruitment period may result in a shortage of resources possibly impacting the quality of the trial, limit the institutional capacity to start new RCTs, can postpone the availability of beneficial interventions, permit harmful or ineffective interventions to remain in use for longer than ethically warranted, thus hindering a conclusion with sufficient statistical power[3].

Premature termination due to poor recruitment has been estimated to occur in 9-10% of all RCTs[4-6]. Variables that have been associated with poor recruitment leading to premature termination are an overestimation of the number of eligible patients, a preference for one of the interventions by the patients, a high burden of the tested intervention for the patients, an unclear trial design, strict eligibility criteria, a lack of logistic support or a lack of funding[7-10]. While the variables that may result in poor recruitment leading to premature termination of the trial are known, much less is known on variables related to recruitment failure within the pre-planned study period, leading to extension of the study period.

The one study to investigate this matter, explored factors associated with recruitment in a cohort of 114 multicentre RCTs in more than nine clinical areas, including cancer, cardiology and obstetrics and gynaecology (18 RCTs had a clinical area classified as ‘other’), and was funded by two public bodies in the United Kingdom; the UK Medical Research Council (MRC) and the Health Technology Assessment (HTA) Programme[6]. RCTs that were funded by the MRC (as compared with the HTA) and were in the clinical area ‘cancer’, had better chances of good recruitment, which was a marginally statistically significant association. The vast

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heterogeneity of RCTs included in that study hampered the identification of other variables associated with poor recruitment and did not allow the authors to provide useful advice for improvement.

To assess factors that are associated with recruitment failure within the pre-planned study period, we performed a nationwide cohort study of RCTs within the homogeneous setting of the Dutch Consortium of Obstetrics and Gynaecology in the Netherlands. Such knowledge is crucial for researchers, trial centres and funding agencies to prevent this type of recruitment failure.

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Methods

Study design

This study was designed as a nationwide cohort study and included all multicentre RCTs carried out within the Dutch Consortium for Women's Health Research, embedded within the professional society, i.e. Dutch Society of Obstetrics and Gynaecology (NVOG)[11]. The Dutch Consortium for Women's Health Research facilitated studies in obstetrics, gynaecology and reproductive medicine.

Within the Consortium, participating clinical centres are both academic and non-academic hospitals. RCTs conducted within the Consortium are supported by a clinical trial centre (https://zorgevaluatienederland.nl/), a multidisciplinary trial bureau with methodologists, data managers, contract managers and trial managers. The trial centre staff supports research groups by advising on the budget, logistics, methods, and ethics approval, developing electronic case record forms, performing contract management and monitoring, creating the interim reports for the data safety and monitoring board and providing advice on the statistical analyses. The findings in our manuscript were reported according to the STROBE guideline[12].

Study population

We included finalized multicentre RCTs supported by the clinical trial centre and performed within the Dutch Consortium for Women's Health Research, between March 1st 2003 and December 1st 2023. We excluded studies with an observational design, single centre RCTs, RCTs initiated outside the Netherlands, RCTs with a cluster or parallel study design, RCTs that never actually started, RCTs in which inclusion of patients was still ongoing and RCTs prematurely discontinued for other reasons than poor recruitment, for example due to safety issues after an interim analysis.

Outcome measures

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Main outcome was recruitment target not achieved within 6 months after the pre-planned recruitment period. These RCTs were defined as RCTs with recruitment failure. The pre-planned recruitment period was documented by the principal investigator before the start of the trial. Secondary outcomes included recruitment target not achieved within an extension period of at least 12 months and premature termination of the trial (defined as stopping with including patients before the recruitment target was achieved). All studies that recruited during the COVID-19 pandemic received 6 months extension of their recruitment period.
In all RCTs, we collected information on variables with a potential effect on recruitment failure, identified after a scoping review. We recorded variables at five levels; patient, doctor, participating centre, study organisation and study design (Appendix 1).

Statistical analysis

For the primary outcome, we used the planned recruitment period as documented in the General Assessment and Registration form, a form that needs to be submitted to the ethical committee before actual start of the study. If we could not get access to this form, we retrieved this information from the main investigator and/or used the data mentioned in the protocol of the study. The actual recruitment period was calculated as the time between the first and last inclusion date.
We checked the continuous potential variables with spline curve analysis. We dichotomised on basis of the spline curve and used the median when the spline suggested a straight line.
We used univariable logistic regression to evaluate the association between potential variables of recruitment failure and expressed these as odds ratios (OR) with corresponding 95% confidence intervals (CI).
To further explore the most relevant risk factors for recruitment failure multivariable risk prediction modelling was done by using both forward and backward stepwise logistic regression including all predictors at once (entry p=0.2 and exclusion p=0.1) and expressed these as adjusted ORs with 95% CI.
We used SPSS® (IBM 2019, USA) software for all statistical analyses (version 25).

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Ethics approval

Our study focussed on logistics and design issues and did not include patients as study participants. Consequently, we did not need ethical approval for this study.

Transparency statement

All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication. The manuscript is an honest, accurate and transparent account of the study being reported, no important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

Role of the funding source

This study was supported by a small departmental grant from the Centre for Reproductive Medicine, Amsterdam University Medical Centres, location AMC.

Public and patient involvement

No patients or members of the public were involved in this study.

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Results

Between March 1st 2003 and December 1st 2023 189 studies started recruitment and were assessed for eligibility. Of these, 106 studies did not fulfil our inclusion criteria, such that in total 83 RCTs were included in the analyses (Figure 1). Characteristics of the included studies are summarized in Table 1. Fifteen RCTs did not have funding at all (18%). A more detailed list of all RCTs can be found as supplementary file Appendix 2[13-89].

Primary and secondary outcomes

In total, 46 of 83 RCTs (55%) did not achieve their targeted recruitment within the pre-planned study period with a maximal extension period of 6 months (Table 2). Recruitment was not achieved within the pre-planned study period with a maximal extension period of 12 months in 41 RCTs (49%). Of these 41 RCTs, 29 studies had a total recruitment period of up to five years, and 12 RCTs finished their recruitment within five to ten years.

Nineteen RCTs (23%) stopped prematurely due to recruitment issues. Of these 19 RCTs, four studies reached 0 to 10% of their recruitment target, six studies 10 to 20%, two studies 20 to 30%, five studies 30 to 60% and two studies reached 70 to 80% of their planned recruitment target.

The mean recruitment period was 50 months (range 12-96 months) for RCTs with recruitment failure versus 31 months (range 12-91 months) for RCTs without recruitment failure. Twenty-two RCTs had a recruitment period of over 48 months. The actual absolute recruitment rate was 4.5 inclusions per month in RCTs with recruitment failure compared to 18.5 inclusions per month in RCTs without recruitment failure ($p<0.001$).

Potential variables of recruitment failure

The association of the potential variables with RCTs with recruitment failure i.e. RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 6 months, is shown in Table 3.

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Variables associated with higher chances on recruitment failure were presence of a no-treatment arm, having a design with more than two arms, a compensation fee of less than 200 euros per included patient, funding of less than 350 000 euros and having more than four inclusion criteria. One variable associated with lower chances on recruitment failure was a preceding pilot study. The most relevant variables for recruitment failure in multivariable risk prediction modelling were presence of a no-treatment arm (OR 4.95, 95% CI 1.18 to 20.80), a compensation fee of less than 200 euros per included patient (OR 2.90, 95% CI 1.02 to 8.25)), funding of less than 350 000 euros (OR 2.99, 95% CI 1.05 to 8.51), while a preceding pilot study lowered the risk for treatment failure (OR 0.21, 95% CI 0.05 to 0.83). When we compared the 41 RCTs that did not achieve their recruitment target within the pre-planned study period with a maximal extension period of 12 months, with the 42 RCTs that completed recruitment within that period, the described associations with treatment failure remained comparable in direction and size.

The most relevant variables for stopping prematurely were the absence of a preceding pilot study and having a no-treatment arm. None of the 19 RCTs that stopped prematurely had performed a pilot study (0%), compared to 17 of the 62 RCTs that completed recruitment (27%). Ten of the 19 RCTs that stopped prematurely had a no-treatment arm (52%), compared to eight of the 64 RCTs that completed recruitment (12.5%) (OR 6.13, 95% CI 1.98 to 19.06).

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Discussion

Main findings

In this nationwide cohort study, 46 of 83 included RCTs (55%) did not achieve their recruitment target within the pre-planned study period with a maximal extension period of six months. RCTs that had a no-treatment arm, low funding and low financial compensation per included patient were at risk to experience this type of recruitment failure, while a preceding pilot study lowered this risk. Upon extension of the pre-planned study period from six to twelve months, 41 RCTs (49%) still did not achieve the pre-planned recruitment target. Nineteen RCTs (23%) were stopped prematurely because of recruitment issues.

Strenghts and limitations

Our study has a number of strengths. First, we investigated recruitment failure in 83 RCTs embedded within the infrastructure of the Dutch Consortium for Women's Health Research – and thus within one homogeneous discipline – with support and monitoring by the clinical trial centre. This allowed us to standardize several important aspects, like trial management and logistics, data collection and data monitoring. Second, we were able to assess all variables with a potential association with poor recruitment as described in literature; type of investigation, placebo-controlled study, treatment versus no treatment, whether the intervention was new or only available in the trial, whether the study was blinded or if there were any competing RCTs, number of study arms, number of inclusion and exclusion criteria, whether a pilot study was performed, number of participating centres and funding and compensation per included patient.

The main limitation of our study is the number of trials. Obviously, if we could have accessed an even larger cohort of trials, we might have been able to identify more potential variables for recruitment failure. Furthermore, our study was done within a standardized setting which may limit the generalisability as many RCTs are conducted in settings without such an infrastructure. A further limitation may be that within our study we focussed on objective variables, such as trial logistics and design issues. Other aspects, like patients' or

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practitioners' perspectives, which may affect recruitment as well were beyond the scope of our study.

In our trials, when the target number of patients was high, the prevalence was high as well. When writing up our protocol, it was decided that this prevalence should not be an input variable. We did an post-hoc analysis and found no impact of target number on failure.

Interpretation

The design of a no-treatment arm where treatment is standard clinical practice was associated with recruitment failure. This design is particularly relevant, since we may be over-treating patients while we are actually in equipoise on whether the intervention is effective at all. Possibly, in this design specifically, the preference of the doctor or patient might play a role in the laborious recruitment. A no-treatment arm was also associated with stopping prematurely, supporting its relevance as a risk factor. In our study ten (52%) of 19 RCTs that stopped prematurely had a no-treatment arm where in current clinical practice treatment is expected.

Not very surprisingly, the lack of funding and compensation fee per included patient (lack of funding and low funding) were associated with recruitment failure. Twelve studies with recruitment failure had no funding at all, compared with three studies without recruitment failure. Along with our finding that extending the recruitment period from six to twelve months did only slightly increase the number of RCTs achieving their pre-planned sample size, this has significant clinical, logistical, and financial implications.RCTs may reach their recruitment target, but in 12 RCTs in our study, recruitment took up to ten years. It implies that when recruitment is doomed to fail, it may reach its required sample size in the end, but at the expense of a lot of endurance and extra funding by a willing sponsor. On the other hand, RCTs can still be of extreme clinical importance if the research question is – and remains – relevant. This is shown by a trial that investigated low-molecular-weight heparin in women with recurrent pregnancy loss and inherited thrombophilia, which took seven and a halfe years years to recruit, but results were eagerly awaited and eventually published in a high impact journal[15].

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A preceding pilot study lowers recruitment failure, while a study design with more than two arms or more than four inclusion criteria might increase the chance of recruitment failure, although with a wide confidence interval, perhaps due to small numbers. We believe that conducting a preliminary pilot study can help identify and address potential challenges before the actual study begins. Our results furthermore suggest that a study design involving more than two arms or over four inclusion criteria may complicate the recruitment process excessively. In a review of the literature on factors limiting the quality and progress of RCTs not hampered by recruitment failure, a straightforward study protocol and data collection as well as careful planning were also identified as key factors for completion[90].

A competing study was not associated with a lower chance on recruitment failure, which is the opposite of what we expected. We hypothesize that when more RCTs in the same field are recruiting patients at the same time, clinicians are more aware of the possibility of including patients in a particular RCT, or when one RCT recruits rapidly, this might be "contagious" for the other RCTs.

It is important to note that our results should not withhold clinicians from conducting RCTs. Investigating the efficacy and safety of treatments and providing robust evidence can be of the utmost importance. Although it is known that the results of randomised and non-randomised studies have a good correlation, non-randomised studies tend to show larger treatment effects, and thus observational studies can be good adjunct to RCTs, but they cannot replace them[91, 92]. More importantly, our study shows that also RCTs with recruitment that takes many years may answer highly relevant clinical questions and can truly make a big difference in the clinical field. Principal investigators, sponsors and all who are participating in an RCT should be aware of the variables associated with poor recruitment, and that with dedication and persistence the RCT could be successfully completed and published.

Further research on how to improve recruitment efforts and increase the success of obstetrical and gynecological RCTs is needed. It would also be relevant to explore

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differences in infrastructure and funding rules and whether these influence recruitment success. Additionally, future research should investigate the perspectives of both patients and practitioners on why participants decline to join RCTs. This research could consider factors such as treatment preferences, as well as patients' fear, anxiety, mistrust in research, and challenges faced by low-income and non-English-speaking groups.

Conclusion

To conclude, RCTs with a no-treatment arm, low funding and low financial compensation per included patient are more likely to experience recruitment failure, while a preceding pilot study lowers this chance. We propose that investigators and grant providers consider these issues before the actual recruitment start of the study, to improve the chances of recruitment success. If a relevant trial is destined to have a suspected long recruitment period, it seems wise to ponder on the question whether to start the trial, or to accept a longer recruitment period with all its consequences.

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Disclosure of interest:

MG reports department research and educational grants from Guerbet and Ferring (location VUmc) outside the submitted work. BWM reports grants from NHMRC, personal fees from ObsEva, personal fees from Merck KGaA, personal fees from Guerbet, personal fees from iGenomix, outside the submitted work. The other authors report no competing interests.

Contribution to Authorship:

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JFWR, MvW, MCW and RGD conceived the study. JFWR and RC did the scope review, selected the potential variables, and collected the data. Differences of opinion and questions regarding the data were resolved with MvW. JFWR was responsible for the data. JFWR, RC and MvW analysed the data. JFWR, MvW, MG and FvdV drafted the manuscript, supported by BWM. All authors contributed to the critical revision of the paper and approved the final manuscript. MvW is responsible for the overall content as guarantor.

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Figure legends

Figure 1. Flow diagram of studies
Table 1. Characteristics of the included studies
Table 2. Recruitment details in the studies with recruitment failure and those with successful recruitment
Table 3. Association with potential variables
Appendix 1. List of variables recorded at five levels
Appendix 2. Detailed list of all included studies

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Table 1. Characteristics of the included studies

Characteristic	n (%)
Research area	
Obstetrics	32 (38)
Reproductive medicine	28 (34)
Oncology	5 (6)
(Uro)gynaecology	18 (22)
Tested intervention	
Drugs	20 (24)
Surgery	20 (24)
Infertility treatments	20 (24)
Obstetrical treatments	12 (15)
Gynaecological treatments	2 (2.4)
Diagnostic strategy	6 (7.2)
Tested intervention	
Existing intervention	69 (83)
New intervention	14 (17)
Tested intervention	
Only available in study	17 (20)
Available outside study	66 (80)
Blinding	18 (22)
No blinding	65 (78)
Number of arms	
2	77 (93)
>2	6 (7)
Pilot study	17 (20)
No pilot study	66 (80)
Recruiting centres	
Only Dutch centres	70 (84)
Including foreign centres	13 (16)
Funding	68 (82)
No funding	15 (18)

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Table 2. Recruitment details in the studies with recruitment failure and those with successful recruitment

	Recruitment failure (n=46)		No recruitment failure (n=37)		p-value
Actual recruitment in years, mean (SD)	50	(20)	31	(12)	<0.001
0 – 1 years, n (%)	2	(5)	1	(3)	<0.001
1 – 2 years, n (%)	3	(5)	6	(16)	
2 – 3 years, n (%)	8	(18)	24	(69)	
3 – 4 years, n (%)	14	(29)	6	(13)	
> 4 years, n (%)	19	(45)	0	0	
Actual recruitment rate/month median (range)	4.5	(0.33 – 39)	18.5	(4 – 189)	<0.001

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Table 3. Association with potential variables

	Recruitment					
	Failure (n=46)		No failure (n=37)		OR (95% CI)	Adjusted OR (95% CI)*
Variables potentially associated with higher recruitment failure						
No treatment arm**	15	(33%)	3	(8%)	**5.48 (1.45 – 20.77)**	**4.95 (1.18 – 20.80)**
Arms > 2	5	(11%)	1	(3%)	4.39 (0.49 – 39.35)	
No funding vs funding	12	(26%)	3	(8%)	**4.00 (1.04 –15.45)**	
Compensation < €200	30	(65%)	12	(32%)	**3.91 (1.56 – 9.78)**	**2.90 (1.02 – 8.21)**
Funding < €350 000	31	(67%)	13	(35%)	**3.82 (1.53 – 9.52)**	**2.99 (1.05 – 8.52)**
Inclusion criteria > 4	17	(37%)	6	(16%)	**3.03 (1.05 – 8.74)**	
Participating centres > 25	17	(38%)	12	(32%)	1.27 (0.51 – 3.16)	
Surgical intervention	14	(30%)	9	(24%)	1.17 (0.72 – 1.90)	
Variables potentially associated with lower recruitment failure						
Pilot study	4	(9%)	13	(35%)	**0.18 (0.05 – 0.60)**	**0.21 (0.05 – 0.88)**
New intervention	5	(11%)	9	(24%)	0.38 (0.12 – 1.25)	
Competing studies***	11	(24%)	13	(35%)	0.58 (0.22 – 1.51)	
Blinding	8	(17%)	10	(27%)	0.57 (0.20 – 1.63)	
Exclusion criteria < 5	23	(50%)	23	(58%)	0.82 (0.32 – 2.09)	
Intervention available only in trial	9	(20%)	8	(22%)	0.88 (0.30 – 2.57)	

Data are in n (%)
*Applying both forward and backward step-wise logistic regression on all variables (entry p>0.2, exclusion p>0.1)
**In these randomised controlled trials (RCTs) no treatment was provided, when in daily practice, treatment was the standard
***During the recruitment phase of these RCTs, there was another RCT that recruited patients with the same inclusion criteria

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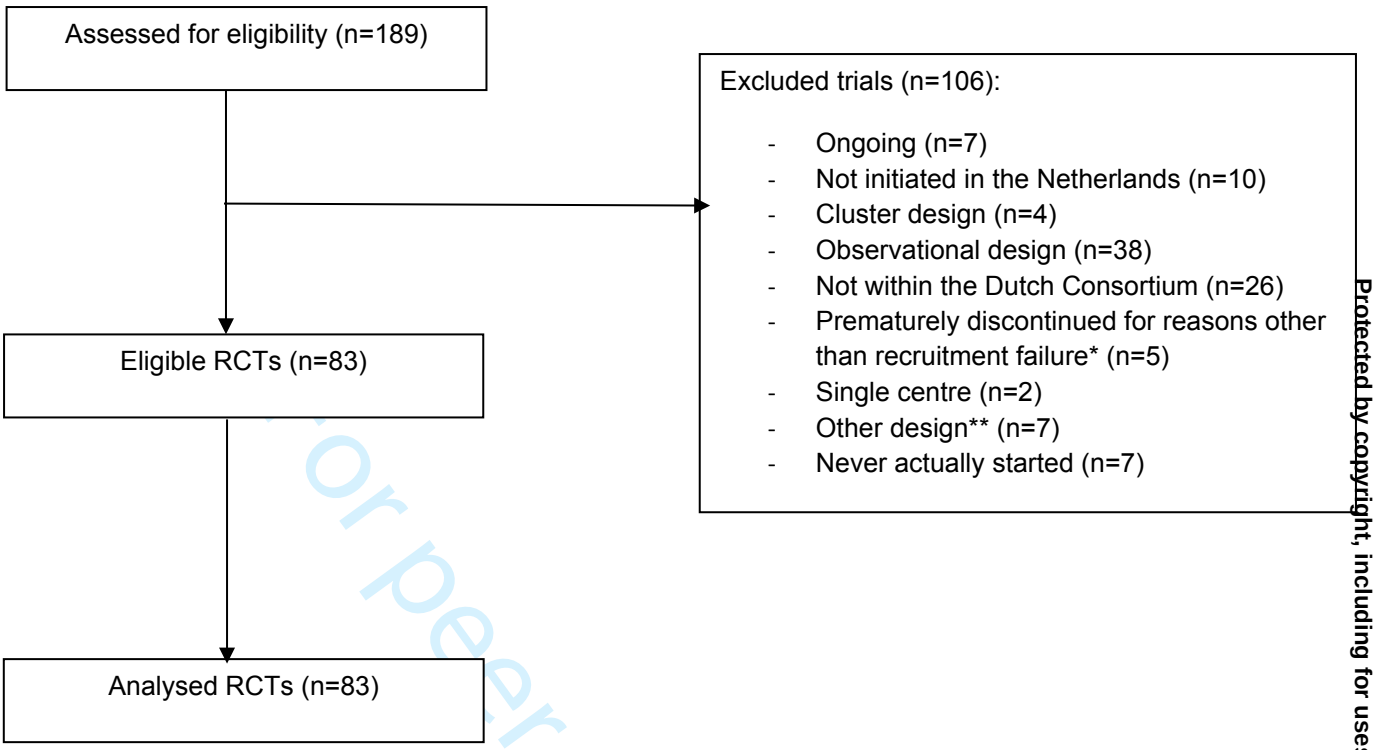
Figure 1. Flow diagram of studies



*In four studies on advice of the Data Safety Monitoring Board due to potential safety issues, and in one study because of revised insights based on new evidence.

**One study was a follow-up study of an RCT, three were implementation studies, one was a study to develop a decision tool, and one was a preference study.

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Appendix 1. List of variables recorded at five levels

Level	Variable
Patient	Were patients blinded or non-blinded
Doctor	Financial reimbursement for including patients
Participating centre	Setting (hospital, primary care, mixed)
Study organisation	Number of participating centres
	International versus national study
	Publication of results
	Funding
	Was the intervention new or existing (common practice)?
	Was the intervention only available in the study setting?
	Was there a competing study during the recruitment phase (including the same study population within the same timeframe)?
Study design	Was there a pilot study?
	Original and final sample size
	Subspecialisation
	Arms of the study
	Intervention type (surgery, medication, treatment)
	No treatment arm where treatment was the standard
	Placebo controlled
	Number of inclusion criteria
	Number of exclusion criteria

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Appendix 2. Detailed list of all included studies

Name study	Study population	Tested intervention	Comparison 1	Comparison 2	Publication	Funding in euros
Studies with recruitment failure						
Obstetrics						
APOSTEL-IV	Women with preterm pre-labour rupture of membranes without contractions 24-34 weeks	Drugs	Nifidipine	Placebo	EJOG Repr Biology 2016	0
APOSTEL VIII	Women with threatened preterm birth (gestational age 30-34 weeks)	Obstetrical treatments	Treatment with atosiban for 48 hours	Placebo	Not yet (analyzing data)	1 400 000
DIGITAT	Women with intra-uterine growth restriction beyond 36 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	BMJ 2010	400 000
GLUCOMOMS	Pregnant women with type 1 or 2 diabetes undergoing insulin therapy <16 or > 30 weeks	Obstetrical treatments	Intermittent use of retrospective continuous glucose monitoring	Standard treatment	Diabetes Obes Metab 2018	300 000
HighLow	Pregnant women with a history of venous thromboembolism	Drugs	Weigh-adjusted intermediate-dose heparin	Fixed low-dose low-molecular-weight heparin	Lancet 2022	1 600 000
HYPITAT-II	Women with non-severe hypertensive disorders of pregnancy 34-37 weeks gestation	Obstetrical treatments	Immediate delivery (induction of labour or caesarean section)	Expectant management until 37 weeks of gestation	Lancet 2015	355 432
INDEX	Low risk women with an uncomplicated singleton pregnancy at 41 weeks	Obstetrical treatments	Induction of labour	Expectant management until 42 weeks	BMJ 2019	670 870
IUPC	Women in whom induced or augmented labour was required	Obstetrical treatments	Internal tocodynamometry	External monitoring	NEJM 2010	0

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PPROMEXIL-3	Women with a singleton pregnancy and preterm pre-labour rupture of the membranes 16-24 weeks gestation with oligohydramnios	Obstetrical treatments	Transabdominal amnion infusion	No intervention	Obstetrics & Gynecology 2019	No funding
QP singletons	Women with a short cervix < 35mm in a singleton and < 38 mm in a multiple pregnancy	Obstetrical treatments	Cervical pessary	Progesterone	Submitted	No funding
SIMPLE-III	Term nulliparous women with a singleton pregnancy and a child in cephalic presentation and the Freidman partogram action line is crossed after regular interventions	Obstetrical treatments	Caesarean section	Expectant management waiting until the simple partogram line is crossed	Unpublished	397 220
STOPORGO	Pregnant women gestational age < 16 weeks who use SSRIs without clinically relevant depressive symptoms	Drugs	Preventive cognitive therapy with gradual guided discontinuation of SSRIs under medical management	Continue use of SSRIs	J Clin Psychiatry 2020	500 000
Sugardip	Women with GDM who do not reach target glycaemic control with modification of diet 16-34 weeks gestation	Drugs	Oral glucose lowering drugs	Insulin	Submitted	437 148
TOTEM	Women with severe preeclampsia 28-34 weeks	Obstetrical treatments	Induction of labour	Expectant management	Acta Obstetricia et Gynecologica Scandinavica 2020	0
TRIPLE P	Women with a singleton pregnancy without a history of preterm birth and a cervix length ≤ 30 mm	Drugs	Progesterone	Placebo	Am J Perinatol 2015	1 000 000

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WOMB	Women with acute anaemia 12-24 hours postpartum without severe anaemic symptoms or comorbidities	Obstetrical treatments	Red blood cell transfusion	Expectant management	BJOG 2014	214 450
Reproductive medicine						
AID	Women who were eligible for donor sperm treatment with cryopreserved donor semen	Fertility treatments	Intracervical insemination with cryopreserved donor sperm	Intrauterine insemination	Human Reproduction 2021	276 000
ALIFE	Women with a history of unexplained recurrent pregnancy loss	Drugs	Aspirin*	Placebo	NEJM 2010	112 500
ALIFE2	Women with recurrent pregnancy loss and inherited thrombophilia	Drugs	Low-molecular-weight heparin + standard treatment	Standard treatment	Lancet 2023	1 200 000
COSY	Heterosexual couples diagnosed with (relatively) unexplained subfertility and a good prognosis	Fertility treatments	6 month web-based interactive educational programme of sex counselling	Expectant management	Submitted	300 000
DESH	Women aged 18-41 years with uni- or bilateral ultrasound visible hydrosalpinges who were scheduled for an IVF/ICSI treatment	Fertility treatment	Hysteroscopic proximal occlusion by intratubal device placement	Laparoscopic salpingectomy	Human Reproduction 2016	0
ESEP	Women with a laparoscopically confirmed tubal pregnancy and a healthy contralateral tube	Surgery	Salpingotomy	Salpingectomy	Lancet 2014	63 000
EX-IUI	Heterosexual couples with unexplained subfertility and a poor	Fertility treatments	6 months IUI with ovarian stimulation	6 months expectant management	Human Reproduction 2022	423 827

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	prognosis for natural conception					
FOAM	Infertile women who were scheduled for tubal patency testing during fertility work-up	Diagnostic strategies	Hysterosalpingo-foam sonography	Hysterosalpingography	Human Reproduction 2022	214 340
H2OLIE	Infertile women who were undergoing hysterosalpingography	Diagnostic strategies	Oil-based contrast	Water-based contrast	NEJM 2017	0
IVF38	Subfertile couples diagnosed with unexplained or mild male subfertility in which the women are 38-42 years old	Fertility treatments	IVF treatment	Expectant management	Manuscript in preparation	365 000
M-OVIN	Women with normogonadotropic anovulation not pregnant after six ovulatory cycles of clomiphene citrate	Drugs	Six cycles of gondadotrophines***	Six cycles of clomiphene citrate**	Lancet 2019	305 000
MASTER 1	Subfertile couples with male subfertility pre-wash total motile sperm count 3-10 x 10^6	Fertility treatments	IUI	Expectant management	Manuscript in preparation	388 208
MASTER 2	Subfertile couples with male subfertility pre-was total motile sperm count < 3 x 10^6	Fertility treatments	ICSI	IVF	Manuscript in preparation	388 208
MEDIUM2	Subfertile couples undergoing an IVF/ICSI treatment	Fertility treatments	Culture medium G5 to culture all oocytes and resulting embryos of each patient	Culture medium CSCM	Manuscript in preparation	0
MISOREST	Women who had primary misoprostol treatment for miscarriage with sonographic evidence of incomplete evacuation of	Obstetrical treatment	Curettage	Expectant management	Human Reproduction 2016	216 000

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	the uterus					
SCRATCH OFO	Women with unexplained infertility and a good prognosis for spontaneous conception	Fertility treatment	Endometrial scratching in the luteal phase of the natural cycle	Expectant management	Manuscript in preparation	349 732
SOMA	Premenopausal women with pain and an ovarian endometrioma	Surgery	Medication	Surgery	Not yet	393 000
STIM	Women 18-43 years with breast cancer who opted for banking of oocytes or embryos	Drugs	Ovarian stimulation**** plus tamoxifen	Standard ovarian stimulation	Human Reproduction 2022	300 000
T4life	Women who were TPO-Ab positive 2 or more pregnancy losses and TSH normal range	Drugs	Levothyroxine	Placebo	Lancet Diabetes Endocrinol 2022	205 983
TRUST	Women with a septate uterus and a wish to conceive	Surgery	Uterine septum resection	Expectant management	Human Reproduction 2021	322 430
Oncology						
LAPOVCA	Patients with suspected advanced-stage ovarian cancer who qualified for primary cytoreductive surgery	Surgery	Laparoscopy	Primary cytoreductive surgery	J Clin Oncol 2016	322 430
PARIS	Women undergoing pelvic radiotherapy	Diagnostic strategies	Chondrotoin sulphate solution	Placebo	Unpublished	3 000
SOCCER	Women with recurrent platinum-sensitive epithelial ovarian cancer	Surgery	Secondary cytoreductive surgery + chemotherapy	Chemotherapy alone	Unpublished	0
(Uro)gynaecology						
CUPIDO-II	Women with a prolapse and occult stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	Int Urogynecol J 2016	24 000

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HYSNICHE	Women with postmenstrual spotting after a cesarean section and a niche with a residual myometrium of at least 3 mm during sonohysterography	Surgery	Hysteroscopic resection of the niche	Expectant management	BJOG 2017	250 000
PEOPLE	Treatment naïve women with pelvic organ prolapse who present with moderate to severe symptoms	Surgery	Pessary therapy	Vaginal pelvic organ prolapse surgery	JAMA 2022	387 000
POMPOEN	Women with postmenopausal bleeding an endometrial thickness > 4 mm and benign result from endometrial sampling	Diagnostic	Further diagnostic workup by hysteroscopy (preceded by saline infusion sonography)	Expectant management	BJOG 2016	0
PROSECCO	Women with a maximum of 3 symptomatic type 0 or 1 submucosal fibroids with maximum 3.5 cm diameter	Surgery	Hysteroscopic myomectomy procedural sedation and analgesia with propofol in outpatient setting	General anaesthesia A operating theatre	Submitted	337 747
SALTO	Women with a history of hysterectomy presenting with symptomatic vaginal vault prolapse with or without concomitant cystocele and rectocele who chose to undergo surgery	Surgery	Laparoscopic sacrocolpopexy	Open abdominal sacrocolpopexy	nt Urogynaecol J 2017	350 000
VUSIS-I	Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Diagnostic strategies	Stress urinary incontinence therapy based on history clinical examination pad test and 48h voiding diary	Therapy based on the same parameters AND urodynamic findings	Neurourol Urodyn 2012	151 000

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WOMAN	Women with a symptomatic cyst or abscess of the Bartholin gland	Gynaecological treatment	Treatment with Word catheter	Marsupialisation	BJOG 2016	0
Studies without recruitment failure						
Obstetrics						
2CLOSE	Caesarean section	Surgery	Single layer uterine closure	Double layer uterine closure	BJOG 2021	359 143
ALLO	Women in labour at term with clinical indices of foetal hypoxia prompting immediate delivery	Drugs	Allopurinol	Placebo	Arch Dis Child Fetal Neonatal Ed 2015	124 576
AMPHIA	Women with a multiple pregnancy	Drugs	Progesterone injections	Placebo	Obstetrics & Gynecology 2011	400 000
APOSTEL-I	Women with symptoms of preterm labour 24-34 weeks negative fibronectin test	Drugs	Nifedipine	Placebo	Am J Perinatol 2015	286 413
APOSTEL-II	Women with threatened preterm labour 26-32 weeks after tocolysis and corticosteroids 48 hours	Drugs	Nifedipine for 12 days	Placebo	JAMA 2013	316 168
APOSTEL-III	Women with threatened preterm birth 25-34 weeks	Drugs	Nifidipine	Atosiban	Lancet 2016	320 000
APRIL	Women with a singleton pregnancy and history of spontaneous preterm birth of singleton between 22 and 37 weeks	Drugs	Low dose aspirin	Placebo	PLOS Med 2022	351 898
HYPITAT	Women with a singleton pregnancy 36-41 weeks with gestational hypertension or mild pre-eclampsia	Obstetrical treatments	Induction of labour	Expectant management	Lancet 2009	380 000

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MOTHER	Women with hyperemesis gravidarum	Obstetrical treatments	Enteral tube feeding	Standard care	Am J Clin Nutr 2017	1 000
PPROMEXIL	Non-labouring women with > 24h preterm pre-labour rupture of membranes 34-37 weeks gestation	Obstetrical treatments	Induction of labour	Expectant management	PLos medicine 2012	600 000
PPROMEXIL-2	Non-labouring women with preterm pre-labour rupture of membranes	Obstetrical treatments	Induction of labour	Expectant management	Am J Obstet Gynecol 2012	600 000
PROBAAT	Women with an unfavourable cervix	Obstetrical treatments	Foley catheter	Vaginal prostaglandin E2 gel	Lancet 2011	0
PROBAAT-II	Women with a term singleton pregnancy and an unfavourable cervix	Obstetrical treatments	Foley catheter	Misoprostol	Lancet 2016	80 000
PROTWIN	Women with a multiple pregnancy 12-20 weeks gestation	Obstetrical treatments	Cervical pessary	Control group	Lancet 2013	313 399
RAVEL	Women with an intermediate to high obstetric risk with an intention to deliver vaginally	Obstetrical treatment	Pain relief strategy with patient controlled remifentanil	Epidural analgesia	BMJ 2015	450 000
STAN	Labouring women with a high-risk singleton pregnancy in cephalic presentation beyond 36 weeks of gestation	Obstetrical treatments	Monitoring by cardiotocography with ST analysis	Cardiotocography only	Obstetrics & Gynecology 2010	400 000
Reproductive medicine						
Antarctica2	Timing frozen embryo transfers	Fertility treatments	Home-based monitoring of ovulation	Hospital-controlled monitoring	Lancet 2023	599 375
BEDREST	Women having intrauterine insemination	Fertility treatments	15 minutes of immobilisation after insemination	Immediate immobilisation	BMJ 2009	0
INES	Couples seeking fertility treatment unexplained	Fertility treatments	Three cycles of in vitro fertilisation with	Six cycles of in vitro fertilisation in a	BMJ 2015	374 116

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	or mild male subfertility		single embryo transfer	modified natural cycle**		
INSIGHT	Women with a normal transvaginal ultrasound of the uterine cavity who were scheduled for their first IVF treatment	Surgery	Hysteroscopy with treatment of detected intra-cavity abnormalities before start IVF	Immediate start of IVF	Lancet 2016	474 147
LIFESTYLE	Infertile women with a BMI of 29 or higher who did not conceive naturally	Fertility treatments	6 month lifestyle-intervention program preceding 18 months of infertility treatment	Prompt infertility treatment	NEJM 2016	766 000
OPTIMIST	Women initiating IVF/ICSI	Drugs	Dose adjustment according to AFC	Standard dose	Human Reproduction 2017	480 000
SCRATCH	Women with one previous failed IVF/ICSI treatment and planning a second fresh IVF/ICSI treatment	Surgery	Endometrium scratching	Standard treatment	Human Reproduction 2021	550 899
SelecTimo	Couples undergoing in-vitro fertilisation or intracytoplasmic sperm injection	Fertility treatments	Time-lapse routine or early embryo viability assessment	Standard treatment	Lancet 2023	650 000
SUPER	Couples diagnosed with unexplained subfertility and scheduled for a maximum of four cycles of IUI with ovarian stimulation	Drugs	FSH	Clomiphene citrate	Human Reproduction 2018	314 310
TOF	Women under 43 years receiving a IVF/ICSI treatment	Fertility treatments	Blastocyst stage (day 5) embryo transfer	Cleavage stage (day 3) embryo transfer	Submitted	700 000
Oncology						
TLH	Women with stage I endometrioid adenocarcinoma or	Surgery	Total laparoscopic hysterectomy	Total abdominal hysterectomy	Lancet 2010	400 000

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	complex atypical hyperplasia					
Vaccin	Adult female patients diagnosed with (histologically proven) CIN II-III and treated with LEEP and no prior vaccination for HPV	Drugs	HPV vaccination	Placebo	Awaiting follow-up	Unknown
(Uro)gynaecology						
CUPIDO-I	Women with a prolapse and evident stress incontinence	Surgery	Prolapse and concomitant anti-incontinence surgery	Prolapse surgery	BJOG 2015	0
EVA	Postmenopausal women undergoing primary pelvic organ prolapse surgery POP-Q stage > 2	Drugs	Vaginal oestrogen cream	Placebo	Manuscript in preparation	250 000
MIRA1	Women with heavy menstrual bleeding without intracavitary pathology	Gynaecological treatments	Levonorgestrel releasing intrauterine system (Mirena)	Bipolar radiofrequency endometrial ablation (Novasure)	Am J Obstet Gynecol 2021	409 270
MIRA2	Women with heavy menstrual bleeding who opt for treatment with endometrial ablation	Surgery	Endometrial ablation plus LNG-IUS	Endometrial ablation	Manuscript in preparation	473 852
PORTRET	Women with stress urinary incontinence	Surgery	Physiotherapy	Midurethral-sling surgery	NEJM 2013	400 000
SAM	Women with symptomatic POP in any stage uterine descent and POP point D < minus 1 cm	Surgery	Sacrospinous hysteropexy	Modified Manchester surgery	JAMA 2023	489 891
SAVE U	Women with uterine prolapse stage 2 or higher requiring surgery and no history of pelvic floor surgery	Surgery	Sacrospinous hysteropexy	Vaginal hysterectomy with suspension of the uterosacral ligaments	BMJ 2015	Unknown

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VUSIS-II	Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered	Surgery/diagnostic strategy	Surgical therapy	Any other therapy (surgical therapy or conservative treatments) as based on individual findings	Neurourol Urodyn 2012	151 000

*with or without nadroparin **or six cycles of intrauterine insemination with ovarian hyper stimulation ***with intrauterine insemination or intercourse ****plus tamoxifen or letrozol

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