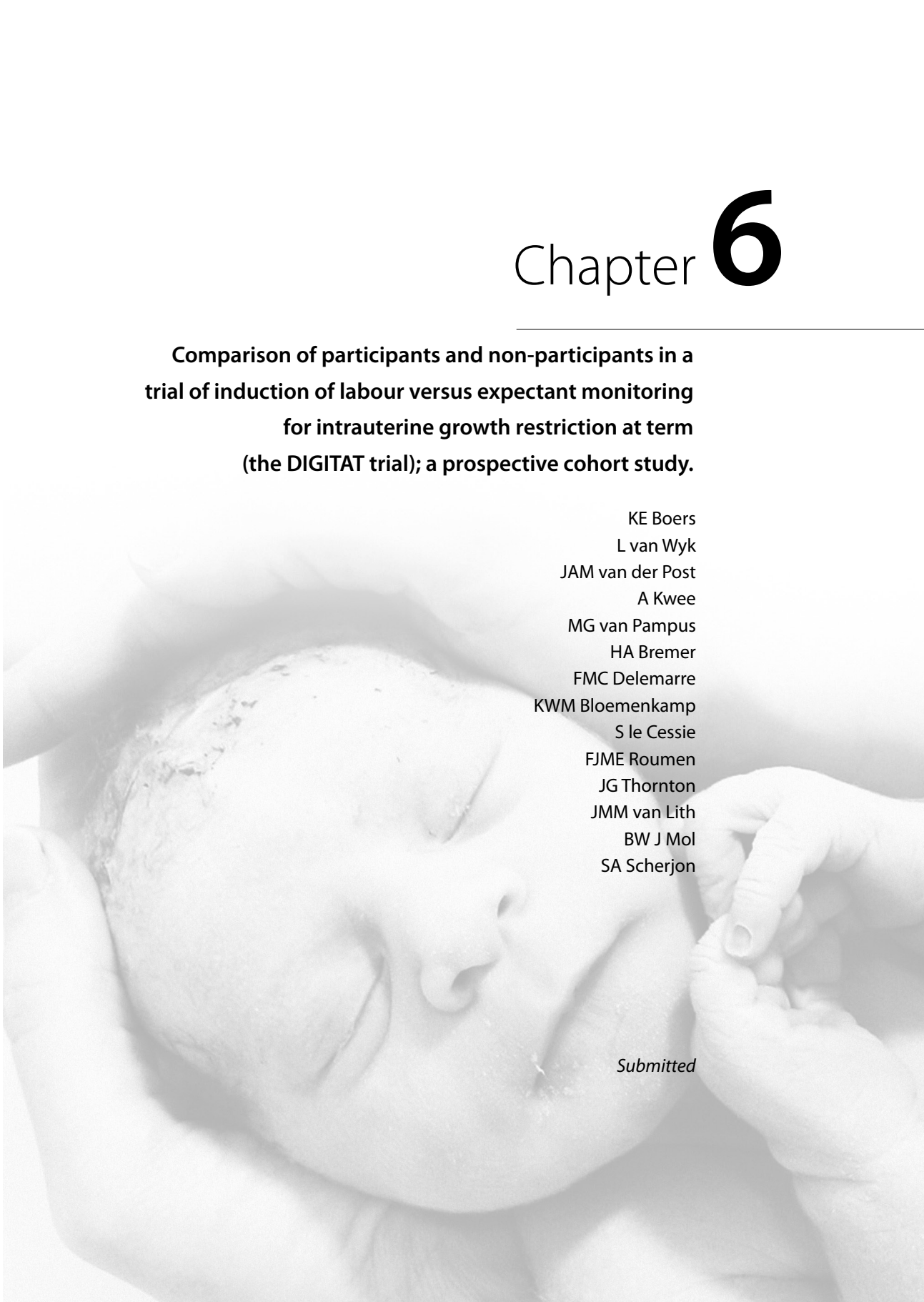
# Chapter 6

**Comparison of participants and non-participants in a trial of induction of labour versus expectant monitoring for intrauterine growth restriction at term (the DIGITAT trial); a prospective cohort study.**

KE Boers
L van Wyk
JAM van der Post
A Kwee
MG van Pampus
HA Bremer
FMC Delemarre
KWM Bloemenkamp
S le Cessie
FJME Roumen
JG Thornton
JMM van Lith
BW J Mol
SA Scherjon



*Submitted*

## Abstract

**Objective:** The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) compared induction with expectant management for pregnant women with a suspected growth restricted foetus at term. To measure the external validity of the trial we compared trial participants outcomes with those of non-participants.

**Design:** Secondary analysis of a randomised equivalence trial (The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT).

**Setting:** Eight academic and 44 non-academic hospitals in the Netherlands between November 2004 and November 2008.

**Participants:** Pregnant women who had a singleton pregnancy beyond 36+0 weeks' gestation with suspected intrauterine growth restriction and participated in the DIGITAT trial, and all patients who declined randomisation, but gave authorisation for the use of their medical data. Identical data were collected prospectively.

**Main outcome measures:** A composite measure of adverse neonatal outcome (neonatal death before hospital discharge, a 5-minute Apgar score < 7, an umbilical artery pH <7·05 or admission to the neonatal intensive care unit), and operative delivery. Comparisons are between participants and non-participants, regardless of the group they are randomised to or treatment received. Propensity scores are used to adjust for baseline differences between the groups.

**Results:** 650 women were randomised and 452 declined. Non-participants were older, had a lower body mass index (BMI), smoked less frequently and had a higher level of education.
A total of 37 (6%) infants of participants experienced the composite adverse neonatal outcome, compared with 32 (8%) among non-participants (adjusted differ-

ence -2.0% (95% CI -5.2% to 1.1%)). Among non-participants 3 (0.7%) deaths (2 stillbirths, 1 neonatal death) occurred, compared with none in the randomised women (difference -0.7% (95% CI -1.4% to 0.1%), p=0.06). Caesarean sections were performed on 90 (14%) participants and on 71 (16%) non-participants (adjusted difference -2.8% (95% CI -7.5% to 1.8%)). After adjustment for baseline imbalances in maternal age, smoking, BMI, education level and hypertensive disorders the adjusted difference and (95% CI) for perinatal death after participation in the trial was -0.5% ((-1.4% to 0.4%), p=0.27)).

**Conclusions:** We found a tendency towards better outcomes in participants, even after adjusting for baseline characteristics. Participation in a randomised clinical trial may be good for you.

## Introduction

Around 80% of intrauterine growth restricted (IUGR) infants of nulliparae are born at term.[1] Such pregnancies are associated with increased neonatal mortality and short and long term morbidity.[2-8] The DIGITAT trial compared labour induction with expectant monitoring in these pregnancies and showed no important differences in maternal or neonatal outcome.[9-10]

Randomised controlled trials (RCTs) must be internally valid, but to be clinically useful the result must also be relevant to a definable group of patients in a particular clinical setting. Lack of consideration of external validity is the most frequent criticism of RCTs.[11-12] Factors influencing external validity include selection of participating centres and recruitment from primary, secondary or tertiary care. Patient factors affecting external validity include eligibility, exclusion criteria, pre-randomisation diagnosis and the percentage of patients that were non-randomised. Factors related to participation in trials are widely discussed [11-13-15] and women's choice to participate is influenced by preferences and socio-economical background.[13-16-] This inclusion bias might decrease the generalisability of the trial findings.

We used the data of non-participants to assess their characteristics and clinical outcomes and to compare these outcomes to patients who consented to randomisation during the trial. By this means we aimed to determine generalisability of the study outcomes and to detect harmful effects of trial participation.

## Methods

### *Study design and patients*

The design of the DIGITAT trial has been described elsewhere.[9] In short pregnant women between 36+0 and 41+0 weeks' gestation who had a singleton fetus in cephalic presentation with suspected intrauterine growth restriction were randomised between induction of labour or expectant monitoring. Suspected intrauterine growth restriction was defined as fetal abdominal circumference below the

10th percentile, estimated fetal weight below the 10th percentile, flattening of the growth curve in the third trimester, or the presence of all three factors.
The trial was run by the Dutch Obstetric Consortium, a collaboration of perinatal centres in the Netherlands, and approved by the University of Leiden institutional review board. Teaching, academic, as well as non-teaching hospitals participated to the trial.
Eligible patients who declined randomisation, but agreed the use of their medical data, were treated according to local protocols at the discretion of the attending obstetrician. Data were collected the same way as for the participants.
Patients who refused randomisation either had induction of labour or an expectant monitoring strategy. The appropriate strategy was in that case elected by the attending obstetrician based on his experience considering the maternal and fetal condition, guided by the preferences of both doctor and patient and local protocols. In the expectant monitoring group of participants labour started either spontaneously, or was initiated by induction for obstetrical indications such as suspected fetal distress, prolonged rupture of membranes, or post maturity between T+7 and T+14 days at the obstetrician's discretion or planned caesarean section.

***Statistical analyses***

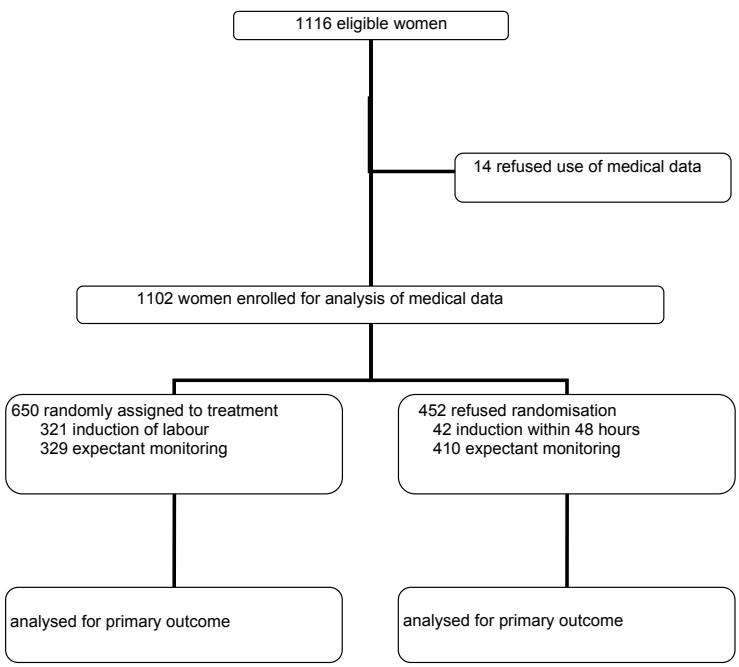
PContinuous variables were summarized as medians with interquartile ranges (IQR). Treatment effects were presented as differences in means or in percentages with 95% confidence intervals (CI). Continuous variables were compared using the Student's t-test or the nonparametric Mann-Whitney U test. The chi-square test and the Fisher exact test were used for categorical variables. If more than 5% of the observations were missing, this is indicated in the footnote of the table. Propensity score methods were used to adjust for group imbalances.[17] The propensity score was calculated for all patients based on the demographic and baseline characteristics using logistic regression. Mean differences and risk differences were adjusted for the propensity score in linear regression models and additive risk models. Multiple imputation was used to handle missing data in the baseline variables. Statistical analysis was performed using SPSS software (version 16•0, Chicago, IL), and R

(version 2.10.0, R Foundation for Statistical Computing, Vienna, Austria.), using the package MICE.[18]

## Results

Between 2004 and 2008, 1116 women were eligible, of whom 650 were randomised and 466 declined. Of the 466 women who declined, 452 consented for use of their medical data, of which 410 women were initially monitored expectantly, and 42 had induction of labour within 48 hours (Figure 1).
The baseline characteristics of the participants and the non-participants are listed

**Figuur 1**
Flow diagram of the process of the study



in Table 1. Participants compared to non-participants were younger (27 years vs. 31 years, mean difference -3.2; 95% CI (-3.9 to -2.6), p<0.001), had a higher BMI (22 vs. 21, mean difference 1.0, 95% CI (0.4 to 1.6), p=0.001), were less educated (84% lower professional education vs. 62% among non-participants, mean difference 23%, 95% CI (16% to 30%), p<0.001) and smoked more (44% vs. 27%, mean difference in percentage 17, 95% CI 11 to 23, (p<0.001).

Pregnancy outcome and mode of delivery are shown in Table 2. Participants were

**Table 1**
Demographic and baseline characteristics of participants and non-participants patients

| Characteristic | IParticipants (n=650) | Non-participants (n=452) | Difference in percentage or mean (95% CI) |
|---|---|---|---|
| Maternal age | 27 (23 - 31) | 31 (27 - 34) | -3.2 (-3.9 to-2.6) *** |
| Body mass index at study entry | 22 (20-26) | 21 (20-24) | 1.0 (0.4 to 1.6) ** |
| Gestational age | 263 (258 – 269) | 262 (258 – 269) | 0.9 (-1.0 to 2.7) |
| Nulliparous | 383 (58.9) | 275 (60.8) | -1.9 (-7.8 to 3.9) |
| Caucasian ¥ | 507 (82.3) | 344 (73.3) | -1.0 (-5.7 to 3.7) |
| Education § | | | |
| Lower professional | 338 (84.3) | 149 (61.6) | 22.7 (15.6 to 29.8)*** |
| Higher professional | 63 (16) | 93 (38) | -22.7 (-29.8 to -15.6)*** |
| Maternal smoking | 265 (43.8) | 114 (26.9) | 16.9 ( 11.1 to 22.7) *** |
| Blood pressure at booking (mmHg) | | | |
| Systolic | 115 (105-120) | 115 (110-120) | -0.8 (-2.4 to 0.8) |
| Diastolic | 69 (60-75) | 70 (60-75) | -1.2 (-2.4 to -0.1) |
| Blood pressure at study entry (mmHg) | | | |
| Systolic | 120 (110-130) | 120 (110-130) | -0.8 (-2.6 to 0.9) |
| Diastolic | 72 (65-80) | 75 (70-85) | -1.5 (-2.8 to -0.1)* |
| Women with gestational hypertension | 28 (4.3) | 25 (5.5) | -1.2 (-3.8 to 1.4) |
| Women with pre-eclampsia | 45 (6.9) | 27 (6.0) | 0.9 ( -2.0 to 3.9) |
| Foetal abdominal circumference (mm) | 288 (278-297) | 289 (278-298) | 0.9 (-2.1 to 2.3) |
| Foetal abdominal circumference (mm) | 288 (278-297) | 289 (278-298) | 0.9 (-2.1 to 2.3) |

Data are median (IQR 25th-75th percentile) or number (%)
*p<0.05, ** p=0.001, *** p<0.001
¥ (n=616 for participants, n=413 for non-participants)
§ (n=401 for participants, n=242 for non-participants)
(n=605 for participants, n=424 for non-participants)

more often induced, delivered earlier and they tended to deliver spontaneously more often. Significantly more women outside the trial developed gestational hypertension.

Table 3 displays neonatal outcome. More babies of non-participants were severely

**Table 2**
Pregnancy outcome and onset of labour

| | Participants (n=650) | Non-participants (n=452) | Difference in percentage or mean (95% CI) | Adjusted difference in percentage or mean (95% CI) |
|---|---|---|---|---|
| Time between randomisation and onset of labour (days) | 3 (1-11) | 8 (3-17) | -3.6 ( -4.9 to -2.3)** | -4.3 (-5.4 to -3.2)** |
| • Induction | 1 (1-2) | 1 (0-1) | | |
| • Expectant management | 10 (5-16) | 10 (5-18) | | |
| Gestational age at delivery (days) | 271 (263-279) | 275 (268-281) | -3.4 (-4.6 to -2.2) ** | -3.0 (-4.3 to -1.8)** |
| • Induction | 266 (261-271) | 267 (260-273) | | |
| • Expectant management | 277 (269-283) | 276 (269-282) | | |
| **Onset of labour** | | | | |
| Spontaneously | 163 (25.2) | 197 (43.7) | -18.5 (-24.2 to -12.9)** | -19.4 (-25.5 to -13.3)** |
| Planned caesarean section | 13 (2.0) | 13 (2.9) | -0.9 (-2.8 to 1.0) | -1.8 (-3.5 to -0.2)* |
| Induction | 472 (72.8) | 241 (53.4) | 19.4 (13.7 to 25.1)* | 20.9 (14.7 to 27.1)** |
| **Mode of Delivery** | | | | |
| Spontaneously | 506 (77.8) | 328 (72.7) | 5.1 (-0.1 to 11) | 4.9 (-0.7 to 10.6) |
| Vaginal instrumental delivery | 54 (8.3) | 52 (11.5) | -3.2 (-6.8 to 4.1) | -2.0 (-6.0 to 1.0) |
| Caesarean section | 90 (13.8) | 71 (15.7) | -1.9 (-6.2 to 2.4) | -3.2 ( -7.8 to 1.5) |
| **Indications for caesarean section** | | | | |
| Suspected fetal distress (+/- arrest of labour) | 77 (85.6) | 59 (84.3) | 2.5 (-8.9 to 13.8) | - 0.2 (-3.5 to 1.9) |
| Arrest of labour | 7 (7.8) | 5 (7.1) | 0.7 (-7.4 to 8.9) | 1.0 (-8.3 to 10.2) |
| Other | 6 (6.7) | 6 (8.6) | -1.8 (-10.1 to 6.5) | -2.4 (-12.8 to 7.9) |
| **Adverse maternal outcome** | | | | |
| Maternal death | 1 | 0 | | |
| Progression to gestational hypertension | 7 (1.1) | 13 (2.9) | -1.8 (-3.5 to -0.1) | -2.1 (-3.8 to -0.3)* |
| Progression to pre-eclampsia | 38 (5.8) | 38 (8.4) | -2.6 (-5.7 to 0.7) | -1.0 (-4.3 to 2.3) |
| Postpartum haemorrhage | 25 (3.9) | 23 (5.1) | -1.2 (-3.7 to 1.3) | - 0.8 (-3.5 to 2.0) |
| Thrombo embolic events | 0 | 1 | | |
| Placental abruption | 0 | 2 | | |

Data are median (IQR 25th-75th percentile) or number (%). CI denotes confidence interval.
* $p < 0.05$; ** $p < 0.001$

growth-restricted (<2.3). There were no significant differences for the other outcomes, but trends were towards more beneficial outcomes for participants. There were no perinatal deaths among participants while there were three deaths among non-participants. Two deaths occurred after expectant policy at 40+1 and at 41+4 weeks pregnancy, with time to delivery of 11 and 24 days respectively. Post-mortem examination showed that these stillbirths were associated with IUGR. The third child died after induction and emergency caesarean section because of placental abruption at 37+2 days gestational age. The suspicion of IUGR had started at 35+6 weeks pregnancy. This child died after a long hospital admission due to serious complications of severe asphyxia. One woman among participants allocated to induction of labour died at home 10 days after delivery. She had delivered a healthy child vaginally at 38+4 weeks of gestation after spontaneous onset of labour. No cause for her death was found at post-mortem and it was classified as a serious unrelated adverse event. No women in the expectant monitoring group of participants or in the non-participants group died during the study.

**Table 3**
Neonatal outcome

| | **Participants (n=650)** | **Non-participants (n=452)** | **Difference in percentage or mean (95% CI)** | **Adjusted difference in percentage or mean (95% CI)** |
|---|---|---|---|---|
| Birth weight (grams) | 2485 (2235-2750) | 2530 (2270-2810) | -28 (-76 to 19) | -19.2 (-70.9 to 32.5) |
| | | | | |
| **Percentiles** | | | | |
| < P 2.3a | 140 (21.5) | 136 (30.1) | -8.6 (-13.8 to -2.3)** | -8.0 (-13.8 to -0.2)* |
| P 2.3a - P5 | 161 (24.8) | 108 (23.9) | 0.9 (-4.3 to 6.0) | - 0.5 (-6.1 to 5.1) |
| P5 - P10 | 150 (23.1) | 99 (21.9) | 1.2 (-3.8 to 6.2) | 2.6 (-2.9 to 8.0) |
| P10 - P25 | 154 (23.7) | 79 (17.5) | 6.2 (1.4 to 11.0)* | 5.8 (0.6 to 11.1)* |
| | | | | |
| **Composite adverse neonatal outcome** | 37 (5.7) | 32 (7.1) | -1.4 (-4.3 to 1.6) | -2.0 (-5.2 to 1.1) |
| foetal deaths/neonatal deaths | 0 | 3 (0.7) | -0.7 (1.4 to 0.1) | -0.5 (-1.4 to 0.4) |
| Apgar score after 5 minutes <7 | 9 (1.4) | 10 (2.2) | -0.8 (-2.5 to 0.7) | -1.1 (-2.5 to 0.4) |
| Arterial pH <7.05 † | 14 (2.5) | 9 (2.4) | 0.1 (-1.9 to 2.1) | 0.2 (-2.0 to 2.4) |
| Admission to intensive care | | | | |
| | | | | |
| **Neonatal admission** | | | | |
| High care/Medium care | 273 (42.3) | 195 (43.2) | -1.1 (-6.9 to 5.0) | -2.7 (-9.3 to 3.8) |
| Maternal ward | 205 (31.8) | 130 (28.8) | 3.0 (- 2.6 to 8.5) | 2.1 (-3.9 to 8.2) |
| No admission | 145 (22.5) | 110 (24.4) | -1.9 (-7.0 to 3.2) | 1.6 (-3.9 to 7.1) |
| | | | | |
| **Length of stay (days)** | 4 (2-8) | 4 (2-7) | ∓ | 0.3 (-1.0 to 1.6) |

Data are median (IQR 25th-75th percentile) or number (%).
CI denotes confidence interval.
a= severe growth restriction according to Dutch percentiles

* p <0.05, **p <0.001 ∓ p=0.5 (Mann-Whitney test)
† n= 567 for participants, n=377 for non-participants
percentiles according to Dutch fetal growth charts

## Discussion

In this study comparing the clinical course of women diagnosed with suspected growth restriction at term, we could not identify harmful effects from participation in a randomised trial comparing induction and expectant management.

The strength of this study is that data were collected prospectively in an identical way, both from participants and non participants.

Though the median fetal abdominal circumference at baseline was comparable for participants and non-participants we found a higher rate of severely growth restricted children at birth in non-participants. Besides, we found a trend towards less spontaneous deliveries and worse neonatal outcomes (more perinatal mortality and lower Apgar scores).

Non-participants were healthier at baseline on important clinical characteristics (i.e. BMI, educational level and smoking). Although these characteristics are in general associated with better neonatal outcomes,[19] opposite associations have been observed in low birth weight infants, like lower mortality rates in low birth weight infants with smoking mothers.[20] This so-called birth weight paradox can be explained by the fact that smoking causes IUGR in otherwise healthy infants, while IUGR in non-smoking women is caused by other medical reasons. Adjusting for the baseline differences between participants and non-participants did not change the results.

Most non-participants were managed initially with an expectant policy, suggesting that this was the preferred management policy of most obstetricians and women during the trial period.

An important difference between the participants and non-participants is that non-participants probably had a strong preference for one of the two management strategies, while the participants were willing to undergo both strategies.

A possible explanation for declining randomisation could be the fact that women did not want to be induced out of fear for medical interventions. Although fewer women that declined participation were induced, this did not lead to a lower rate of operative deliveries.[21]

Our data are in accord with many other studies which suggest that participation in a randomised trial[22] or protocol driven management[23] improves outcomes regardless of the actual treatment given.[14-16-24] It seems that the DIGITAT women benefited from the protocol-driven attention of their doctors. Moreover women participating in a study are probably also more attentive to their medical status.

Recruitment to clinical trials is influenced by social economic status (SES), and women who are less educated are often less willingly to participate.[25-30] Conversely, in the DIGITAT trial a lower SES led to more participation.

Overall neonatal admission rates were comparable in the two groups, but more children of non-participants were severely growth restricted at birth, probably as a result of a longer expectant time to delivery. This is in accord with results of the DIGITAT trial. The higher rate of severe growth restricted children might explain the tendency towards less favourable outcomes. However, we did not find this association between severely growth restricted children and worse outcomes among children of participants who were managed expectantly.[31]

While none of the children of participating women died, perinatal deaths did occur among non-participants. The mutual factor of these 3 children was a relative long time of expectant management, and 2 of the 3 were delivered only after 40 weeks. These findings might imply that over long prolongation of pregnancy in IUGR imposes perinatal morbidity and mortality, perhaps also due to the lack of protocol driven management.

In conclusion we found a tendency towards more favourable outcomes in women randomised to the DIGITAT trial than in women who refused to participate, even after adjusting for baseline characteristics. Participation in a randomised clinical trial on growth restriction did not increase the risk of bad outcome.

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