

Supplementary Document: Opening research sites in multicentre clinical trials within the UK: A detailed analysis of delays

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Supplementary Table 1: List of available delay reasons for SANADII data collection

A large list of delay reasons was generated to cover a variety of circumstances. All codes were available to use throughout all stages of the site set up process and were not restricted by milestone.

*Where the code included 'specify' a free text field required extra information to be added.

- Not a CTU priority centre
- No response to email
- No response to phone
- Cannot contact site, specify*
- Awaiting update from research network
- SANADII Staff on Annual leave or off-sick
- Research site staff on annual leave and no cover
- Participation discussions ongoing with site
- Feasibility being undertaken by site
- Identification of key contacts, specify if any particularly difficult to identify (e.g. microbiology, pharmacy)*
- Excess Treatment Cost (ETC) Negotiations ongoing
- Commissioner will not fund ETC
- ETC Other, specify*
- Waiting for staff to come into post
- Other general site resource issue, specify*
- Other trial specific site resource issue, specify*
- General Trial Paperwork not complete (by SANADII staff), specify*
- General Trial Supplies outstanding (by SANADII staff), specify*
- Waiting local REC approval (international sites only)
- Waiting for site to populate SSI
- Unable to identify required SSI authorisations i.e. directorate approval and person with authority, specify*
- SSI awaiting signatures from PI
- Waiting for Trust Logo to localise Patient Information Sheet and Consent form (PISC)
- Waiting for site to localise PISC
- Waiting for CVs of team
- R&D Pre Submission Checks
- R&D Pre Submission Check Query, specify*
- Awaiting permission from R&D to submit SSI form
- Additional documentation required specific to an R&D department, specify*
- GCP certificates required by R&D for all staff prior to R&D approval
- R&D query, specify
- Waiting for R&D approval letter
- Awaiting contract feedback from site
- Contract negotiations between site and Sponsor ongoing, specify*
- Unable to identify required contract signatories, specify*
- Contract awaiting signatures from site
- Contract awaiting signatures from sponsors
- Awaiting Material Transfer Agreement (MTA) feedback from site
- MTA negotiation between site and Sponsor ongoing , specify*
- Unable to identify required MTA signatories, specify*

- MTA Awaiting signatures from site
- MTA Awaiting signatures from sponsors
- CTU waiting for delegation log
- CTU waiting GCP certificates
- CTU waiting for acknowledgment of essential documents
- Paperwork lost at site or in the post
- Other documentation outstanding, specify*
- IRAS/ CSP issue, specify*
- Waiting for Laboratory Accreditation Certificate
- Waiting for Laboratory reference ranges
- Change of PI requires new ethical approval
- Compilation of Investigator Site File / Pharmacy File
- Waiting for site staff to undertake GCP training
- Availability of site team for site initiation/ training on trial procedures
- Availability of site team for intervention training
- Waiting for site to roll out intervention training
- Pharmacy funding
- Pharmacy green light
- Intervention Supply issues with manufacturer
- Other, Specify*

Supplementary Table 2: Reasons for Non-Participating SANAD-II sites dropping out.

| | Adult | Paediatrics | Total* |
|--|--------------|--------------------|---------------|
| Excess Treatment Costs | 3 (30.0%) | 2 (11.8%) | 5 (18.5%) |
| Issues with trial drugs | 0 (0.0%) | 1 (5.9%) | 1 (3.7%) |
| Never interested | 0 (0.0%) | 1 (5.9%) | 1 (3.7%) |
| No response | 2 (20.0%) | 2 (11.8%) | 4 (14.8%) |
| Non participation of a key local site | 1 (10.0%) | 2 (11.8%) | 3 (11.1%) |
| PI capacity | 3 (30.0%) | 6 (35.3%) | 9 (33.3%) |
| Resource issues | 1 (10.0%) | 3 (17.7%) | 4 (14.8%) |
| Total | 10 | 17 | 27 |

*5 sites (4 adult and 1 paediatric) that had initially planned to have separate SSI application to other teams within the same trust, proceeded to participate under the SSI application of the other team.

Percentage of dropouts from all included sites

10 out of 57 (17.5%) adult sites* dropped out.

17 out of 60 (28.3%) paediatric sites* dropped out.

* Sites that are now “participating under another site” have been excluded from the calculations.

Supplementary Table 3: Kaplan-Meier Summary table for time from MREC to site opening (months) from Figure 2

Kaplan-Meier summary

| | MREC in 2012 (n=17) | MREC in 2013 (n=111) | Total (n=128) |
|------------------------------|--------------------------------|---------------------------------|--------------------------|
| | (N=15 ^{\$1}) | (N=81 ^{\$2}) | (N=96) |
| 25% quartile (95% CI) | 11.43 (10.48, 12.42) | 6.21 (5.03, 7.49) | 7.33 (5.68, 8.44) |
| Median (95% CI) | 14.49 (10.51, 15.84) | 9.72 (7.56, NR) | 10.48 (9.66, 13.73) |
| 75% quartile (95% CI) | 16.00 (14.49, NR) | NR | 15.15 (14.49, 16.33) |

Notes: ^{\$1}First 17 sites from 2012: 2 excluded as they are not participating. ^{\$2}Rest of sites from 2013: 30 excluded as they are not participating. NR= not reached

| Hazard ratio (95% CI) |
|---|
| Log-rank <i>p</i>-value |
| Rest vs. First 17: 2.32 (1.02, 5.24) <i>p</i> =0.04 |

Supplementary Table 4: Kaplan-Meier Summary tables for time between milestones from Figure 3

Time from MREC approval to SSI Submission for participating sites (months)

Kaplan-Meier summary

| | Total Participating sites (n=96) |
|------------------------------|---|
| | (N=81 [§]) |
| 25% quartile (95% CI) | 4.07 (3.22, 4.90) |
| Median (95% CI) | 7.03 (5.45, 9.59) |
| 75% quartile (95% CI) | 12.32 (9.82, NR) |

Notes: [§]15 excluded (14 are in the first 17 sites, 1 site has a missing SSI submission date). NR= not reached

Time from SSI validation to R&D approval for participating sites (days)

Kaplan-Meier summary

| | Total participating sites (n=96) |
|------------------------------|---|
| | (N=46 [§]) |
| 25% quartile (95% CI) | 5.00 (3.00, 9.00) |
| Median (95% CI) | 16.00 (8.00, 21.00) |
| 75% quartile (95% CI) | 32.00 (21.00, 46.00) |

Notes: [§]50 excluded (31 sites have not submitted SSI, 7 have submitted SSI and not received R&D approval yet but have a missing SSI validation date, 11 have received R&D approval but have a missing SSI validation date, 1 site has a negative time due to technical issues with IRAS)

Time from R&D approval to site open to recruitment for participating sites (days)

Kaplan-Meier summary

| | Total participating sites (n=96) |
|------------------------------|---|
| | (N=56 [§]) |
| 25% quartile (95% CI) | 8.50 (3.00, 12.00) |
| Median (95% CI) | 15.00 (12.00, 23.00) |
| 75% quartile (95% CI) | 40.00 (23.00, 60.00) |

Notes: [§]40 excluded (39 sites have not reached R&D approval and 1 site from the first 17 SANADII sites was excluded as it required ETC approval during NHS restructure)

Supplementary Table 5: Percentage of sites that met 30 day and 70 day targets

a) Proportion of SANAD-II sites that achieved R&D approval within 30 days of a valid SSI:

Of the 96 participating sites, 51 were excluded from the analysis:

- 31 had not yet submitted their SSI form
- 7 Had submitted the SSI and not received R&D approval but had a missing SSI validation date.
- 11 Had submitted the SSI and received R&D approval but had a missing SSI validation date.
- 1 site had a negative time due to technical issues with IRAS
- 1 had their SSI validated on the data download date

33/45 (73%) received R&D approval within 30 days.

b) Proportion of SANAD-II sites that randomised their first patient within 70 days of a valid SSI:

Of the 96 participating sites, 56 were excluded from the analysis:

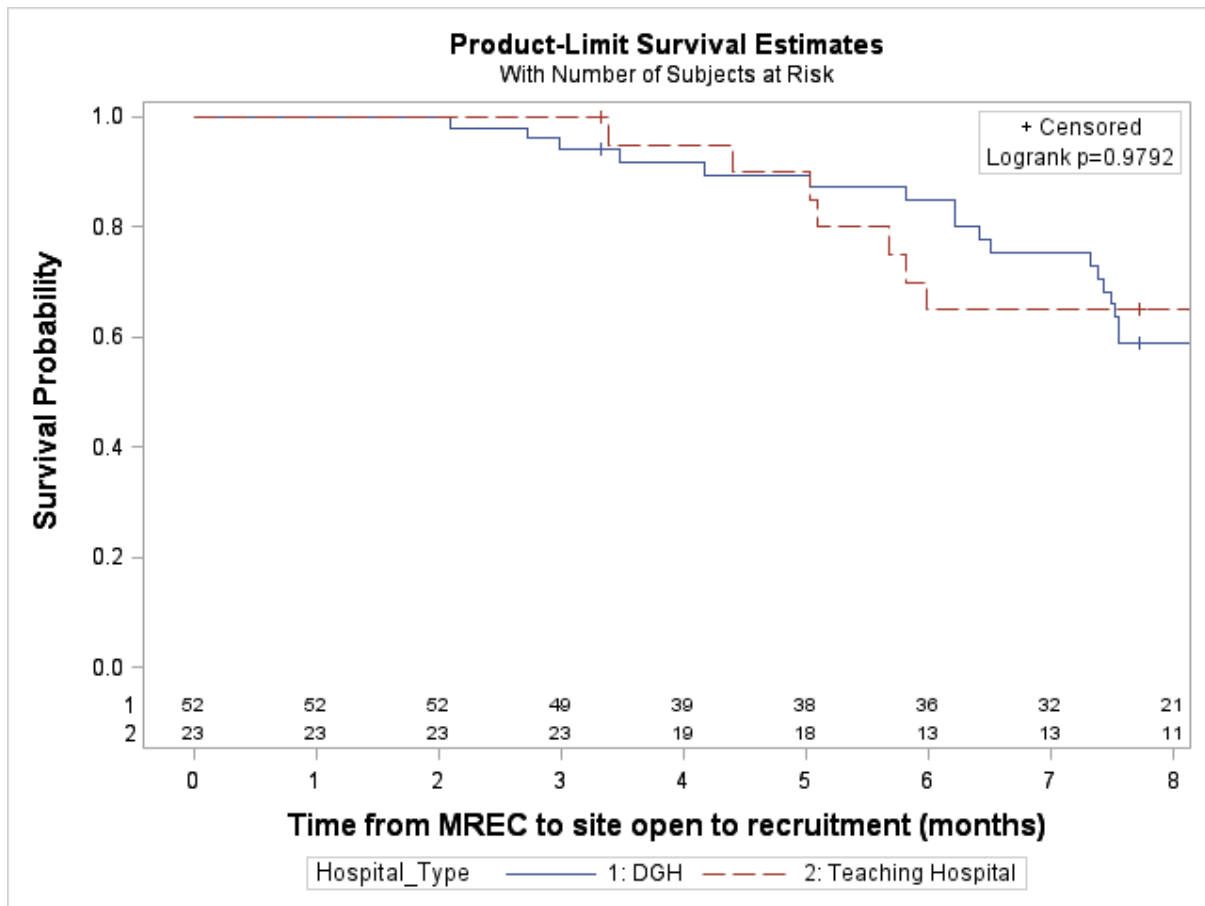
- 31 had not yet submitted their SSI form
- 7 Had submitted the SSI and not received R&D approval but had a missing SSI validation date.
- 11 Had submitted the SSI and received R&D approval but had a missing SSI validation date.
- One of the first 17 sites was excluded as they required ETC approval during the NHS restructure, which caused a unique delay after R&D approval
- 6 have not yet randomised their first patient but were still within the 70 days

(NB sites that had not recruited their first patient but surpassed the 70 days were included)

12/40 (30.0%) sites recruited their first patient within 70 days.

Supplementary Figure 1: Comparison of MREC to site opening to recruitment for different site characteristics

a) Hospital Type

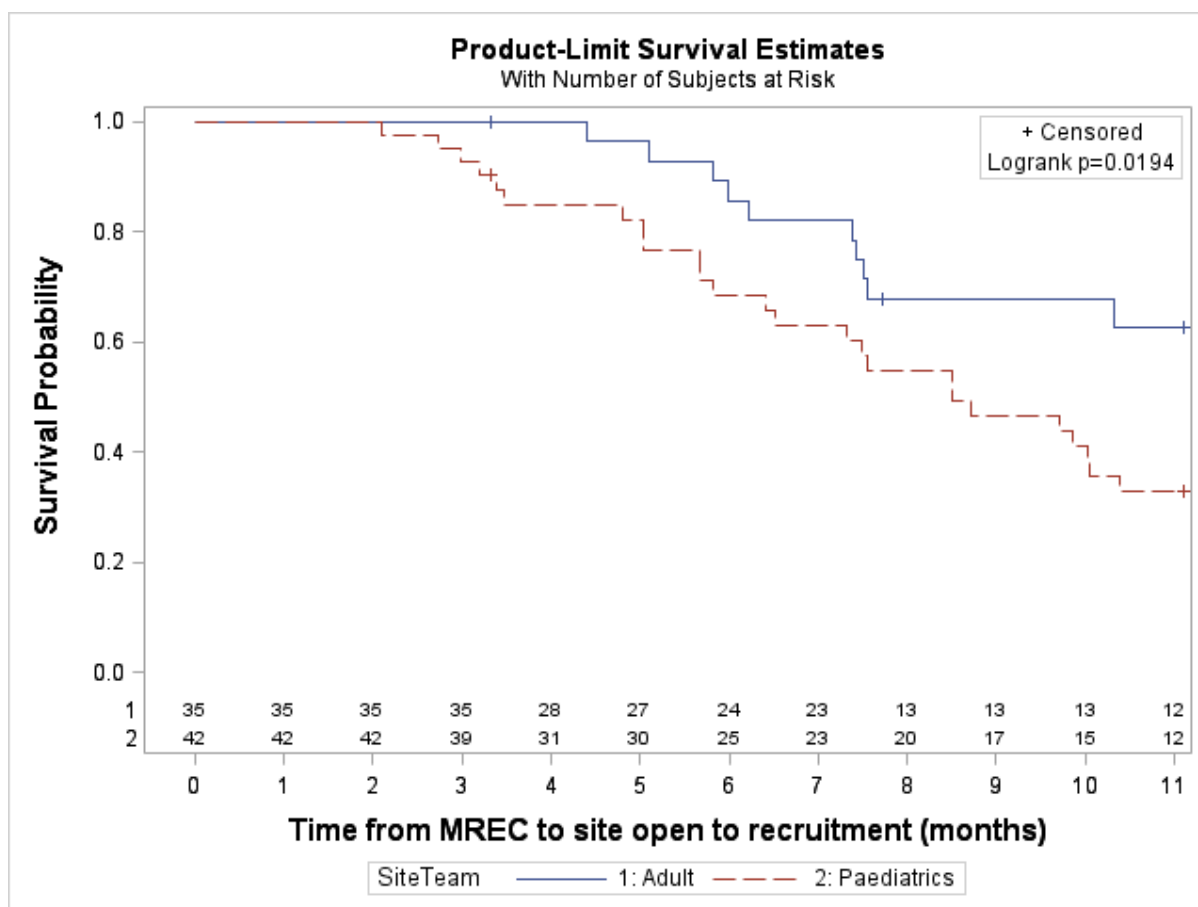


Kaplan-Meier summary

| | Participating District General Hospitals (DGH) (n=56) | Participating Teaching Hospitals (n=31) | Total participating DGH or teaching Hospitals (n=87 [#]) | Hazard ratio (95% CI) Log-rank p-value |
|-----------------------|---|--|--|---|
| 25% quartile (95% CI) | (N=52 ^{S1}) 7.33 (5.03, 7.56) | (N=23 ^{S2}) 5.75 (3.38, 8.71) | (N=75) 6.41 (5.09, 7.52) | Teaching hospital vs. DGH: 0.99 (0.49, 2.02) p=0.98 |
| Median (95% CI) | 10.02 (7.49, NR) | 9.66 (5.68, NR) | 9.72 (7.56, NR) | |
| 75% quartile (95% CI) | NR | NR | NR | |

Notes: [#]2 Health Centres, 6 specialist paediatric sites and 2 specialist tertiary sites excluded due to low numbers in the groups. ^{S1}DGH: 4 excluded as in the first 17 sites. ^{S2}Teaching Hospital: 8 excluded as in the first 17 sites. NR= not reached.

b) Recruitment Type

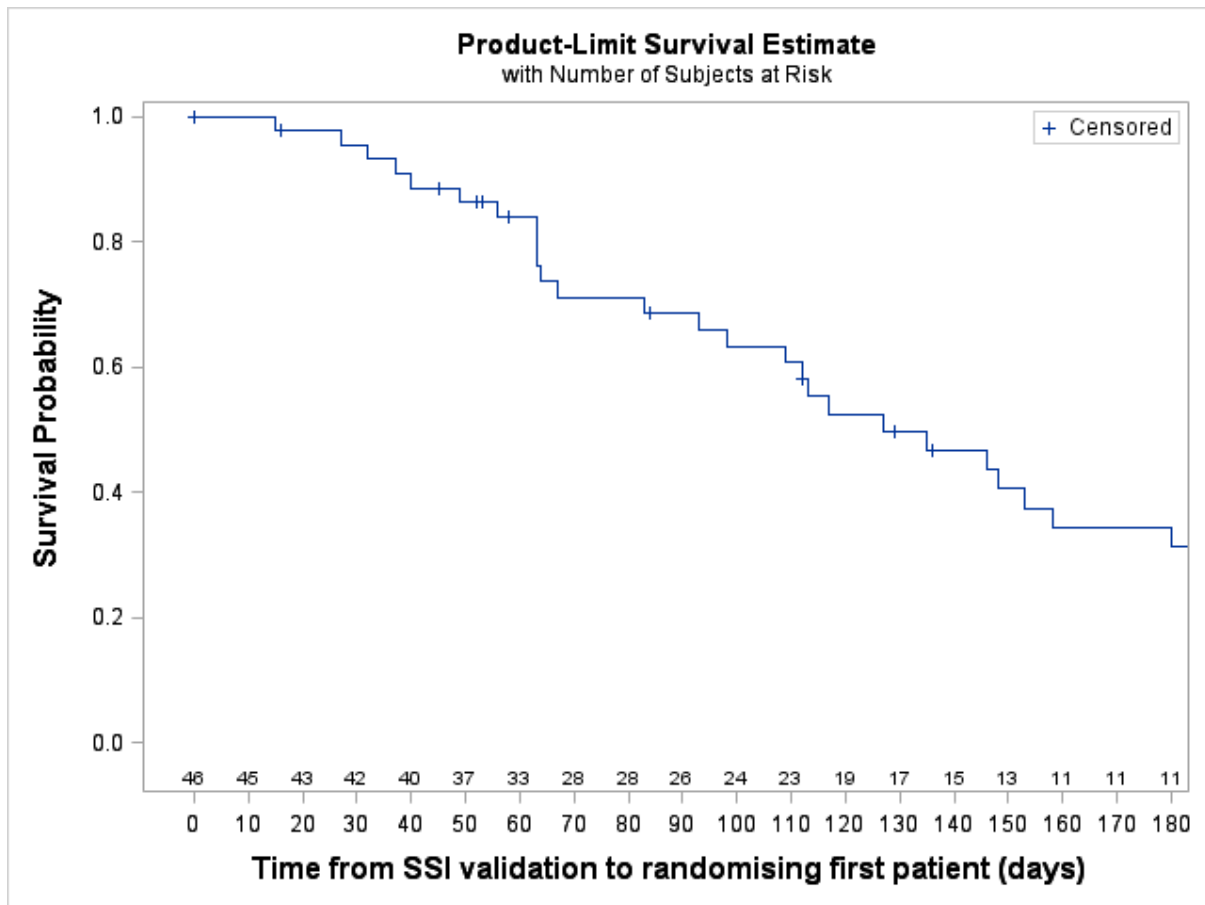


Kaplan-Meier summary

| | Participating Adult sites (n=47) | Participating Paediatric sites (n=43) | Total participating sites (n=90 [#]) | Hazard ratio (95% CI) Log-rank p-value |
|------------------------------|----------------------------------|---------------------------------------|--|---|
| | (N=35 ^{\$1}) | (N=42 ^{\$2}) | (N=77) | Paediatrics vs. Adult: |
| 25% quartile (95% CI) | 7.48 (5.09, NR) | 5.68 (3.38, 7.33) | 6.21 (5.03, 7.52) | 2.33 (1.12, 4.83) |
| Median (95% CI) | NR | 8.51 (6.41, 10.38) | 10.02 (7.56, NR) | p=0.02 |
| 75% quartile (95% CI) | NR | NR | NR | |

Notes: [#]6 sites recruiting both Paediatrics and Adults excluded due to low numbers in group. ^{\$1}Adult: 12 excluded as in the first 17 sites. ^{\$2}Paediatrics: 1 excluded as in the first 17 sites. NR= not reached

Supplementary Figure 2: Time from SSI validation to recruiting and randomising the first patient (days)

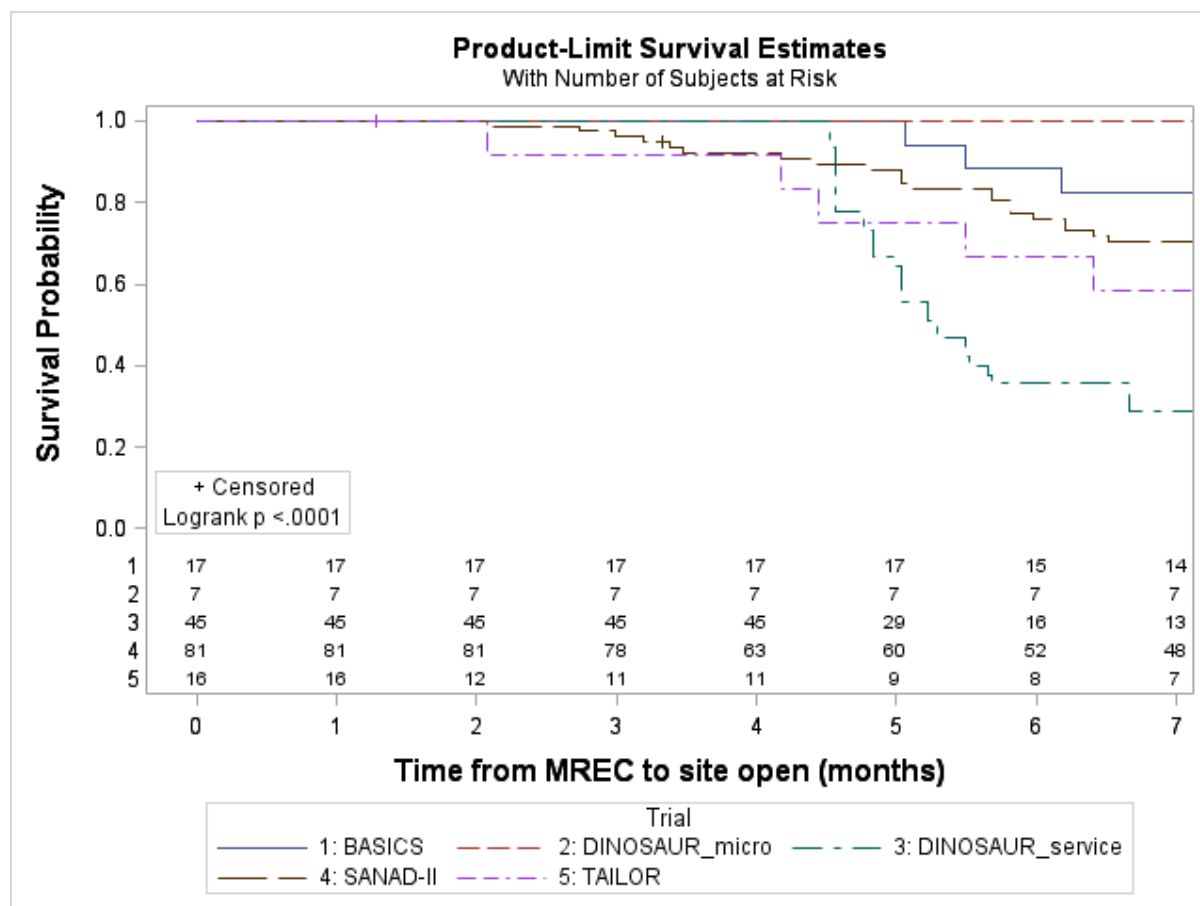


Kaplan-Meier summary

| | Total Participating sites (n=96) |
|------------------------------|---|
| | (N=46 [§]) |
| 25% quartile (95% CI) | 64.00 (40.00, 109.00) |
| Median (95% CI) | 127.00 (93.00, 158.00) |
| 75% quartile (95% CI) | 230.00 (148.00, NR) |

[§]50 excluded (31 sites have not submitted SSI yet, 7 have submitted SSI and not received R&D approval yet but have a missing SSI validation date, 11 have received R&D approval but have a missing SSI validation date, 1 site from the first 17 SANADII sites was excluded as it required ETC approval during NHS restructure). NR= not reached

Supplementary Figure 3: Comparison of time from MREC to Site Opening time for different CTRC trials



Kaplan-Meier summary

| | 1:BASICS (medical device trial) (n=17) | 2:DINOSAUR (Microbiology study) (n=7) | 3:DINOSAUR (Service Evaluation) (n=51) | 4:SANAD-II (n=128) | 5:TAILOR (drug trial) (n=17) | Total (n=220) |
|------------------------------|---|--|---|---|--|---------------------------------|
| 25% quartile (95% CI) | (N=17) 8.64 (5.06, 10.12) | (N=7) 7.98 (7.82, 8.48) | (N=45 ^{S1}) 4.76 (4.57, 5.03) | (N=81 ^{S2}) 6.21 (5.03, 7.49) | (N=16 ^{S3}) 4.97 (2.07, 10.68) | (N=166) 5.22 (4.99, 5.68) |
| Median (95% CI) | 10.74 (8.41, NR) | 8.48 (7.82, 9.20) | 5.29 (4.99, 5.68) | 9.72 (7.56, NR) | 12.54 (4.17, 17.61) | 7.82 (7.36, 8.71) |
| 75% quartile (95% CI) | NR | 9.20 (8.44, 9.20) | 7.36 (5.65, 7.52) | NR | 17.60 (10.68, NR) | 13.73 (10.12, 17.58) |

| Hazard ratio (95% CI) | Log-rank p-value |
|-----------------------------------|------------------|
| 1 vs. SANAD-II: 0.82 (0.41, 1.64) | p<0.0001 |
| 2 vs. SANAD-II: 1.80 (0.79, 4.08) | |
| 3 vs. SANAD-II: 3.63 (2.32, 5.68) | |
| 5 vs. SANAD-II: 0.82 (0.35, 1.95) | |

Notes: ^{S1}DINOSAUR service: 6 excluded (1 site not participating, 5 took longer to open as waiting for DINOSAUR microbiology approval). ^{S2}SANAD-II: 47 excluded (32 sites not participating, 15 sites in the first 17 sites). ^{S3}TAILOR: 1 site excluded as not participating. NR= not reached