9. Appendix

Appendix 1: Survey of PROFILE trial collaborators

We hope to better understand about practices in personalised medicine clinical trials and particularly how to overcome challenges and any barriers to delivery of biomarker-stratified trials. This work is being completed as part of a doctoral thesis on improving efficiency of novel clinical trials by Dr Nuru Noor (funded by a Medical Research Council PhD Studentship).

1. What is your primary working role looking after patients with IBD?
    a. Gastroenterology specialist/consultant
    b. Gastroenterology resident/trainee
    c. Specialist nurse
    d. Research nurse
    e. Other (please describe) _____

2. How many years' experience do you have in any capacity with randomised, interventional, clinical trials in IBD (to nearest figure)?
    a. 0 year
    b. 1-2 years
    c. 3-5 years
    d. 6-10 years
    e. 10+ years

3. Have you ever been a Chief Investigator (clinical lead) for a randomised, interventional clinical trial in IBD?
    a. No
    b. Yes

4. Have you ever been a Principal Investigator (recruitment site lead) for a randomised, interventional clinical trial in IBD?
    a. No
    b. Yes

5. Have you ever been involved in a biomarker-stratified or personalised medicine trial in any other disease area?
    a. No
    b. Yes (please describe area) _____

6. How have you found **explaining** a personalised medicine trial such as PROFILE to patients compared to a classical, parallel, two-arm, interventional clinical trial in IBD?
    a. Easier to explain a personalised medicine trial
    b. No difference
    c. Harder to explain a personalised medicine trial

7. How have you found **recruiting** to a personalised medicine trial such as PROFILE compared to a classical, parallel, two-arm, interventional clinical trial in IBD?
    a. Easier to recruit to biomarker-stratified trial
    b. No difference
    c. Harder to recruit to biomarker-stratified trial

8. Given the biomarker result in PROFILE is double-blinded (result unknown by patient or clinical team looking after patient until the end of the trial). Has this affected your ability to **explain** the PROFILE trial to patients?
    a. No
    b. Yes (please describe) _____
9. Has the double-blinded result affected your ability to **recruit** patients to PROFILE?
    a. No
    b. Yes (please describe) _____

10. Has the double-blinded result affected your ability to **retain** patients to PROFILE?
    a. No
    b. Yes (please describe) _____

11. Before the PROFILE trial opened at your local site, how would you have rated your confidence for understanding and delivering a biomarker-stratified clinical trial?
    a. Very low confidence
    b. Low confidence
    c. Fair confidence
    d. High confidence
    e. Very high confidence

12. Now that the PROFILE trial is open at your local site, how would you rate your confidence for understanding and delivering a biomarker-stratified clinical trial?
    a. Very low confidence
    b. Low confidence
    c. Fair confidence
    d. High confidence
    e. Very high confidence

13. Which of these trials designs and/or platform protocols would you feel comfortable explaining to patients and other research staff? (can select multiple options)
    a. Biomarker/ stratified medicine designs
    b. Adaptive protocols that will add or drop intervention arms during the trial
    c. Platform protocols (addressing more than one primary research question)
    d. None of the above

14. What specific training opportunities would allow the IBD multi-disciplinary community to improve delivery of novel trial designs/platforms in IBD? (can select multiple options)
    a. No specific training required
    b. Specific guidelines for training IBD clinical trial investigators
    c. Mentorship provided by prominent leaders in IBD clinical trials
    d. Confidential observerships of trial oversight committee meetings for IBD trials
    e. Fellowships specifically in IBD clinical trial methodology
    f. Dedicated online interventional clinical trial training course in IBD
    g. Dedicated face-to-face interventional clinical trial training course in IBD
    h. Other (please describe) _____

15. What has been the single biggest challenge encountered at your local site for the PROFILE biomarker-stratified trial?

    _____

16. If you would you be willing to be contacted further to discuss your experiences from participating in a biomarker-stratified medicine trial please provide your email address:

    _____

We are grateful for your time and responses. All data will be anonymised and collated together to help inform future trial conduct in the field. If you have any queries regarding this work then please feel free to contact Nuru Noor: nurulamin.noor.18@ucl.ac.uk.

Appendix 2: Topic guide for interviews with PROFILE trial collaborators

1. Interviewer name	Nurulamin Noor
2. Participant ID#	
3. Interview date (mm/dd/yyyy)	|___|___|/|___|___|/|___|___|___|___|
4. Participant agrees to audiovisual recording	☐ Yes ☐ No
5. Time interview began (hh:mm)	|___|___ | : |___|___| pm
6. Time interview ended (hh:mm)	|___|___| : |___|___| pm

Step 1: Complete Q1—3 above before starting the interview.

Step 2: Introduce yourself at the beginning of the interview.

Step 3: Thank participant for taking part in the interview.

Step 4: Read *Section 1: Information about the study* to the participant.

Step 5: Ask for the participant's permission to record the interview.

Step 6: Press audio recording button if permitted. Document time.

Step 7: Conduct interview.

Step 8: Thank the participant at the end of the interview. Ask if questions.

Step 9: Document time interview ended above.

Step 10: Ask participant if I can contact them in future with results of project.

Appendix 3: Relapse rate, retreatment success and predictors of relapse and retreatment success after anti-TNF discontinuation in Crohn's disease

First author	Sample size	Duration of treatment before withdrawal (median, months)	Criteria for stopping	IMM at stopping	Definition of relapse	Follow-up (range or median, months)	Time to relapse (median, months) and Relapse rate	Retreatment success	Identified Predictors of relapse and strength of prediction -	Identified Predictors of retreatment success and strength of prediction
Systematic reviews/Meta-analysis										

Gisbert JP, 2016[6] And Gisbert JP, 2015[5]	27 studies (23 focused on CD)	At least 6 months (range: 8.5-37)	Heterogeneous	Heterogeneous, ranging from 0 to 100%	NR	Range: 6-125 months	Time to relapse range: 4-16 Relapse rate: 44%, 95% CI 36-51), I^2 79% - Short term (< 12 months) 38%, 95% CI 13-63%, I^2 80% - Medium term (12-24 months): 40%, 95% CI 33-48%, I^2 78% - Long term (> 24 months) 49%, CI 31-68%, I^2 88%	82%, 95% CI 70-95)	**Clinical variables** - Age at diagnosis < 25 years (HR 1.83; 95% CI 1.03–3.25) - Smoking (HR 1.91; 95% CI 1.11–3.27; OR 2.74; 95% CI 0.99–7.59) - Longer disease duration at first biologic administration (HR 1.1; 95% CI 1.0–1.1) - Fistulising perianal CD (incidence of relapse in perianal vs. luminal CD: 65-66% vs. 31-42%) - Patients receiving escalated anti-TNF doses (OR 13; 95% CI 1.39–120) - Patients receiving anti-TNFs for the prevention of post-operative recurrence (Incidence of relapse 83-100%). **Laboratory markers** - Haemoglobin levels <145 g/L (HR 6.0; 95% CI 2.2–16.5) - White cell count >6x10^9/L (HR 2.4; 95% CI 1.2–4.7) - High CRP levels - CRP ≥5 mg/L before stopping therapy → HR 3.2; 95% CI 1.6–6.4	NR

									- at start of therapy → OR 2.38; 95% CI 0.92–6.19 - CRP > 5 mg/L → HR 4.2; 95% CI 1.9–9.2 - High faecal calprotectin - FC ≥ 300 µg/g →HR 2.5; 95% CI 1.1–5.8 - FC > 250 µg/g → HR 6.5; 95% CI 2.7–15.6 - IFX TL ≥2 µg/L (HR 2.5; 95% CI 1.1–5.4)	

Kennedy NA, 2016[47]	12 studies (10 with CD patients), 624 CD patients	At least 12 months	Sustained clinical remission (at least 6 months)	NR	Clinical relapse (studies where endoscopic recurrence was the outcome were excluded)	At least 12 months	Relapse rate: - 1 year: 39% (95% CI 35-44), I^2 12% - 2 years: 24-month 54% (95% CI 49-59), I^2 0%	88% (95% CI 78-95), I^2 64%	**Clinical variables***** - Age at diagnosis < 22 years (HR 2.29; 95% CI 1.35–3.88), p=0.002 - Montreal behaviour B2 (HR 1.60; 95% CI 0.88–2.90), p=0.200 **Laboratory markers at drug withdrawal***** - White cell count >5.25 x 10^9/L (HR 2.06; 95% CI 1.11–3.80), p=0.022 - FC >50 µg/g (HR 2.95; 95% CI 1.22–7.12), p=0.02	NR
Pauwels RWM, 2021[121]	14 studies; 1317 CD patients	At least 6 months (median 23 months, range 14-40)	Steroid-free clinical, biochemical or endoscopic remission for at least 6 months	71%	Need of (re)introduction of biologicals, steroids, IMM or surgery for CD luminal activity or complications	Median: 13 months (7-28)	Relapse rate: - 1 year: 38% (33-42%), I^2 57% - 2-years: 52% (46%-57%), I^2 54%	NA	**Clinical variables** - Clinical remission (HR 0.45; 95% CI 0.24-0.84) - Smoking (HR 1.39; 95% CI 1.15–1.67) - Montreal classification A1 vs A2 (HR 1.47; 95% CI 1.12–1.92) - Montreal location L4 (HR 1.33; 95% CI 0.97–1.82) - Disease duration, every 5 years (HR 1.07; 95% CI 0.98–1.17) - Younger age at anti-TNF cessation, per decade (HR 1.16 95% CI 1.00-1.33)	NA

									- Concomitant IMM (HR 0.70; 95% CI 0.58–0.85) - Second line anti-TNF (HR 1.32; 95% CI 1.01–1.72) - ADA vs IFX (HR 1.21; 95% CI 0.99–1.49) **Laboratory markers** - CRP per doubling (HR 1.04; 95% CI 1.00–1.08) - FC per doubling (HR 0.88; 95% CI 0.61–1.25	
Torres J, 2015[11]	69 studies (40 reporting on withdrawal of anti-TNF, 32 of which in CD)	Heterogeneous data	In most studies in the adult population, anti-TNF discontinued in patients in clinical remission	Not specified in 6 studies, 20 to 100% in the remaining studies	Heterogeneous	Heterogeneous	Relapse rate: 22%-83%	78.3% to 100%	**Clinical variables** - Treatment with an IMM after discontinuation of anti-TNF (HR 0.5; 95% CI 0.3–0.7) **Laboratory markers** - Epidermal growth factor level ≤ 39.5 U/mL (HR, 2.7; 95% CI 1.2–6.6)	NR
Yang S, 2021[39]	9 studies (8 with CD patients); 428 patients	NR	NR	61-100%	NR	Range: 12-52 months	NA	87% (95% CI 83-91%), I^2 4%	NA	NR

Zhang B, 2020[122]	13 studies with 837 patients (CD: 239 patients)	NR	Deep remission (clinical remission and mucosal healing/endoscopic remission)	NR	NR	Range: 11-43 months	**Relapse rate: - 1 year: 29.8% /95% CI 22.4-38.5%) - 2 years: 41.4% (95% CI 36.1-46.9%)	NR	NR	NA
Randomised Controlled Trials										
Buhl S, 2022[26]	115 CD patients (59 continued IFX and 56 discontinued it)	Median: 23 months (16-39) (24 in IFX continuation and 21 in IFX discontinuation group)	Complete remission - clinical (CDAI < 150 points), normal biochemical parameters, endoscopic remission and normal MRI and/or capsule endoscopy – for at least 3 months	54% (32/59) in IFX continuation group and 52% (29/56) in IFX discontinuation group	Clinical (CDAI > 150 with an increase in 70 points from baseline over two consecutive weeks, or definitive clinical relapse requiring immediate intervention judged by treating physician)	Median: 13 months	Time to relapse: 65% (15/23) of the relapses occurred within 100 days after treatment discontinuation. Time to relapse significantly shorter in the IFX discontinuation group than in the IFX continuation group (HR 0.080, 95% CI 0.035-0.186, p<0.001).	NR	**Clinical variables** - Use of concomitant IMM showed a trend toward increased time to relapse	NA

							Week 48 relapse rate: 49% in IFX discontinuation group (vs 0% in IFX continuation group).			
Louis E, 2022[123]*	205 CD patients (Arm A continued combination treatment, arm B stopped IFX, arm C stopped anti-metabolite)	At least 8 months	Steroid free remission > 6 months	100%	CDAI and objective marker of inflammation – CRP or FC	Design: 24 months of follow-up	2-years relapse rate: - Arm A: 14% (CI 95% 4-23%) - Arm B: 40% (CI 95% 28-51%) - Arm C: 10% (CI 95% 2-18%) P=0.0003 arm B vs A and <0.0001 arm B vs C	Arm A: 50% (1/2) Arm B: 96% (22/23) Arm C: 67% (2/3)	NR	NR
Prospective studies										
Brooks AJ, 2017[46]	86 CD patients	Median: 23 months (12-80)	Inactive disease based on clinic, biomarkers, endoscopy and	88% (76/86)	Clinical (recurrent symptoms requiring treatment	Median: 17 months (12-72)	Time to relapse: 7.5 months (1.4-39.5)	93% (26/28)	**Clinical variables** - Previous surgical resection (OR 5.485; 95% CI 1.059–34.992)	NR

			radiology or physician's global assessment		escalation or surgery)		Relapse rate: - 90 days: 4.7% (4/86) - 180 days: 18.6% (16/86) - 365 days: 36% (31/86)	Same anti-TNF: 87% (20/23) Different anti-TNF: 86% (6/7)	- Montreal location L3 vs L1 (OR 3.184; 95% CI 1.149–11.144) - Patients receiving escalated anti-TNF doses (OR 8.513; 95% CI 0.823–203.715)	
Gallego JC, 2017[52]	29 CD patients	Median: 44 months (12–72)	Sustained deep remission: clinical (HBI ≤ 3), endoscopic (SES-CD<2), and analytical (CRP<5 mg/L + FC <150 mg/g for at least 3 months before treatment withdrawal)	100% (18/29 with azathioprine, 6/29 with mercaptopurine, 5/29 with methotrexate)	NR	Median: 45 months (24-72)	Time to relapse: 17 months Relapse rate: - 1 year: 24% - 2 years: 52% (15/29)	NA	**MRE** - MRE score > 3 before withdrawal compared with those showing a score of 0–3 (RR 2.21; 95% CI 1.1–5, p=0.042)	NA
Louis E, 2012[45]	115 CD patients	Median: 26 months (18-37)	Corticosteroid free remission for 6 months (CDAI < 150)	100% (thiopurines or methotrexate)	CDAI > 250 or between 150 and 250 points with a 70-point increase from baseline over 2 consecutive weeks	Median: 28 +- 2 months	Time to relapse: 16 months Relapse rate: - 1 year: 43.9% +- 5%	88% (38/43) in remission and 98% (42/42) with clinical response	**Clinical variables** - Male sex (HR 3.7; 95% CI 1.9–7.4, p<0.001) - Steroid use 12 and 6 months before baseline (HR 3.5; 95% CI 1.1-10.7, p=0.03)	NR

							- 2 years: 52.2% +- 5.2%		- No previous surgical resection (HR 4.0; 95% CI 1.4-11.4, p=0.01) **Laboratory markers:** - Hemoglobin level ≤ 145 g/L (HR 6.0; 95% CI 2.2-16.5, p<0.001) - Leukocyte count > $6x10^9$/L (HR 2.4; 95% CI 1.2-4.7, p=0.01) - hsCRP level ≥ 5mg/L (HR 3.2; 95% CI 1.6-6.4, p<0.001) - IFX TL ≥ 2 mg/L (HR 2.5; 95% CI 1.1-5.4, p=0.02) - FC ≥ 300 µg/g (HR 2.5; 95% CI 1.1-5.8, p=0.04) **Endoscopy** - CDEIS >0 (HR 2.3 ; 95% CI 1.1–4.9, p=0.04)	
Mahmoud R, 2022[37]	81 patients, with 41 CD patients	Median: 50 months (31-96)	Coricosteroid free clinical remission (HBI <5) for > 6 months and endoscopic healing (SES-CD < 5)	26.8% (11/41)	Endoscopic relapse (SES-CD ≥5 or large ulcers) OR clinical (HBI >5 with >3 points increase from baseline) and biochemical (CRP > 10 mg/L or FC >	Median: 24 months	Relapse rate at 12 months: 37% (15/41)	Retreatment success (for IBD in general, based on physician global assessment): - 3 months: 73%	**Endoscopy** **-** partial (versus complete) endoscopic healing (aHR 4.16; 95% CI 1.47 – 11.8, p=0.007)	NR

					250ug/g) relapse OR step-up of medical treatment OR IBD-related hospitalization OR surgery OR newly diagnosed disease complication.			- 12 months: 90%		
Molnar T, 2013[49]	121 CD patients	12 months	One year of maintenance treatment with clinical remission at week 12 (CDAI ≤ 150 points)	85% (103/121) treated with thiopurines, 8,8% stopped during follow-up	Increase of > 100 points in CDAI + CDAI > 150 points	NR	Time to relapse: 6 months (IQR: 3.75-12) 1 year relapse rate: 45% (55/121)	55%	**Clinical variables** - Previous biological therapy (HR 4.23; 95% CI 1.39–12.84)	NR
Rajca S, 2014[55] *(ancillary study of Louis E, 2012)*	33 CD patients	NR	Corticosteroid free remission for 6 months (CDAI < 150)	100% (thiopurines or methotrexate)	CDAI > 250 or between 150 and 250 points with a 70-point increase from baseline over 2 consecutive weeks	NR	NA	NA	**Microbial variables** Decreased counts of *Faecalibacterium prausnitzii* (aHR 4.1; 95% CI 1.2–13.3) and *Bacteroides* (HR 3.3;95% CI 1.1–10.1) independently of high CRP	NA
Rismo R, 2013[54]	37 CD patients	Median: 5 months (2-29)	Clinical remission (CDAI < 150) and endoscopic healing (complete	84% (31/37)	CDAI increase of > 70 points and/or endoscopic findings qualifying for	Range: 0.7 – 41 months	Time to relapse: 6 months Relapse rate:	NA	**Immune variables** - Elevated IL17A in the mucosa (HR 3.3; 95% CI 1.11–9.95, p=0.03)	NA

			mucosal restitution with absence of ulceration and redness)		retreatment with an anti-TNF or steroids		- week 26: 52% (16/31) - week 52: 74% (20/27)		- Elevated TNF in the mucosa (HR 4.3; 95% CI 1.49–12.14, p=0.007)	
Ternant D, 2015[53] *(ancillary study of Louis E, 2012)*	111 CD patients	Median: 26 months (18-37)	Corticosteroid free remission for 6 months (CDAI < 150)	100% (thiopurines or methotrexate)	CDAI > 250 or between 150 and 250 points with a 70-point increase from baseline over 2 consecutive weeks	Median: 28 months	Time to relapse: 16 months Relapse rate: 45% (50/111)	NA	**Genetic markers** - The polymorphism of Fc fragment of IgG, low affinity IIIa, receptor (CD16a) [FCGR3A] influences the risk of relapse after IFX discontinuation. There is an interaction between CRP and the FCGR3A genotype. - In patients with CRP≥5 mg/L, risk of relapse was higher for V/V patients (HR 4.80) than for F carriers (HR 2.84; 95% CI 1.84–4.41)	NA
Retrospective studies										
Baert F, 2014[32]	128 IBD patients (105 with CD) restarting IFX treatment after a minimum drug holiday of 6 months	Median: 12 months (0-92)	Remission, pregnancy, patient decision, loss of response, adverse event	71.4% (75/105)	NA	NR	NA	Week 14: 87.7% (92/105) Year 1: 72.6% (76/105) End of follow up period:	NA	**Clinical variables** - Reinitiation with concomitant IMM therapy associated with short-term response (HR 6, 95% CI 1.3-27, p=0.019) - Pregnancy or remission as reason for discontinuation (versus loss of response and infusion reactions) associated with long-term response (HR 2.70, 95% CI 1.09-6.67, p=0.033) **Laboratory markers**

								63.8% (67/105)		- Antibodies to infliximab after reinitiation associated with short-term response (HR 0.14; 95% CI 0.026-0.74, p=0.021) - Higher trough levels after reinitiation were associated with long-term response (HR 2.94, 95% CI 1.18-7.69, p=0.021) - Undetectable antibodies to infliximab after reinitiation associated with the safety of reinitiating therapy (HR 7.7, 95% CI 1.88-31.3, p=0.004)
Casanova MJ, 2017[48]	1055 patients (731 with CD)	Median: 18 months (12-36) for IBD in general: - Top-down group: 4 months - Elective discontinuation group: 21 months - Adverse events group: 14 months	Physician or patient decision, adverse events, top-down strategy	69% (480/731 thiopurines and 22/731 methotrexate)	Clinical, biochemical, endoscopic or radiological activity leading to a therapeutic intervention	Median: 19 months (6-176) for IBD in general	Time to relapse for IBD in general: 11 months (1-140) Cumulative incidence of relapse for IBD in general: 44% (95% CI 41-46) Relapse rate for CD: 19% per patient-year, 95% CI 17-21	End of follow-up: - remission: 76% (190/250) - partial response: 13% (32/250)	**Clinical variables** - Older age at discontinuation (HR 0.67, 95% CI 0.51-0.87, p=0.003) - Maintenance of IMM after discontinuation of anti-TNF (HR 0.67; 95% CI 0.51–0.87, p=0.003) - ADA vs IFX (HR 1.29; 95% CI 1.01–1.66, p=0.04) - Elective discontinuation vs. discontinuation for top-down strategy (HR 1.90; 95% CI 1.07–3.37, p=0.03) - Discontinuation due to adverse events vs discontinuation for top-down strategy (HR 2.33; 95% CI 1.27–4.29, p=0.006) - Montreal classification (L2 vs L1) (HR 1.51; 95% CI 1.13–2.02, p=0.005)	NR

									- Montreal classification (B2 vs B1) (HR 1.50; 95% CI 1.09-2.05, p=0.01)	
Casanova MJ, 2021[38] *(extension study of Casanova, MJ, 2017)*	1055 patients (731 with CD) – the outcome from 637 patients from Casanova, MJ 2017 was updated	Median: 18 months (IQR 12-36) - Top-down group: 4 months - Elective discontinuation group: 21 months - Adverse events group: 14 months	Physician or patient decision, adverse events, top-down strategy	69% (480/731 thiopurines and 22/731 methotrexate)	Clinical, biochemical, endoscopic or radiological activity leading to a therapeutic intervention	Median: 34 months (IQR:13-73)	Time to relapse for IBD in general: 17 months (IQR 7-42) Cumulative incidence of relapse for IBD in general: 50% (95% CI 47-53) Relapse rate for CD: 13% per patient year (95% CI 12-14)	74% (160/237) treated with the same anti-TNF achieved remission; of these 15% relapsed at the end of follow-up. 13% had a partial response.	**Clinical variables for IBD in general** - Older age at diagnosis (HR 0.98; 95% CI 0.97-0.99, p<0.0001) - Maintenance therapy with IMM at discontinuation (HR 0.64; 95% CI 0.52-0.8, p<0.0001) - Elective discontinuation vs discontinuation for top-down strategy (HR 1.88; 95% CI, 1.20-2.94, p=0.005) - Discontinuation due to adverse events vs discontinuation for top-down strategy (HR 2.01; 95% CI 1.24-3.25, p=0.004).	NR
Chauvin A, 2014[30]	92 CD patients	NR	Stable remission	100%	HBI > 4 or the need to introduce any specific	Median: 47 months (4-110)	Time to relapse: 27 months (8-75)	89% (47/53) at week 8-10, and 72%	**Clinical variables:**	**Other** - IFX failure-free survival was higher in patients who were

			assessed by HBI < 4		treatment for CD		Relapse rate: 72% (66/92)	(38/53) at ~1.2 years	**-** Active smoking (HR 1.91; 95% CI 1.11-3.27, p=0.02 - Previous antimetabolite failure (HR 1.78; 95% CI 1.07-2.97, p=0.03) - Perianal disease (HR 1.72; 95% CI 1.02-2.89, p=0.04)	retreated more than 12 months after IFX withdrawal
Laharie D, 2009[57]	109 CD patients	3.5 months (induction + 1 maintenance infusion)	NA	100% (63/109 thiopurines, 46/109 methotrexate)	Clinical relapse (symptoms of reopening of a healed fistula) and endoscopic, radiographic and/or biological evidence of inflammation.	Median follow-up after retreatment: 25 months	Relapse rate: 56% (61/109)	80% (49/61) clinical benefit at week 4 of retreatment	NR	**Other** - Median time >50 weeks from induction to retreatment predictor of failure (OR 7.38, 95%CI 1.38–39.59, p=0.02)
Papamichael K, 2015[50]	100 CD patients	Median: 7 months (IQR 1.4-16.2)	Sustained clinical remission (based on physician global assessment) without the need to reintroduce medical therapy or surgery	84% (68/100 thiopurines and 16/100 methotrexate)	Need to reintroduce medical therapy or surgery, whenever available confirmed with laboratory tests (CRP), endoscopy and imaging techniques	Median: 116 months (IQR 96-138)	Time to relapse: 55 months (IQR 36-85) Relapse rate at the end of follow-up: 48% (48/100)	NA	**Clinical variables:** **-** Age at diagnosis < 25 years (HR 2.08; 95% CI 1.16-3.7, p=0.012) - Disease duration at the start of IFX > 1 year (HR 2.71; 95% CI 1.2-6.13, p=0.017) **Laboratory markers** - IFX TL > 6 mg/mL at the time of IFX cessation (HR 6.99; 95% CI 1.19–41.15, p=0.031)	NA

									Endoscopy - Presence of ulcerations at the time of IFX cessation (HR 3.95; 95% CI 1.03–15.2, p=0.046)	
Reenaers C, 2018[35] *(follow-up study of Louis E, 2012)*	102 CD patients	Median: 26 months (19-38)	Corticosteroid free remission for 6 months (CDAI < 150)	100%	CDAI > 250 or between 150 and 250 points with a 70-point increase from baseline over 2 consecutive weeks	Median: 83 months (IQR 71-93)	Relapse rate: 78% (80/102)	66% (42/64)	NR	NR
Ten Bokkel Huinink S, 2022[124]	486 CD patients	Median: 49 months (24–79)	Clinical, biochemical or endoscopic remission	36% (153/176 thiopurines and 23/176 methotrexate)	Clinical (presence of symptom or EIM), biochemical (CRP ≥5 mg/l and/or FC ≥250 µg/g), endoscopic (presence of macroscopic inflammation at endoscopy)	Median: 20 months (IQR 9–37)	Time to relapse: 8 months (IQR 4–19) Relapse rate: - 1 year: 35% (31–39%) - 2 years: 54% (49–59%)	81% achieved either clinical response or remission	**Clinical variables:** - younger age at diagnosis (HR 1.5 for A1 vs. A2) - age at cessation (HR 1.2 per 10 years younger) - upper gastrointestinal tract involvement (HR 1.32; 95% CI 0.96-1.79 for L4 vs. non-L4) - clinical symptoms at cessation (HR 2.2) - smoking (HR 1.39; 95% CI 1.15-1.67), - longer disease duration (HR 1.07; 95% CI 0.98-1.17 per 5 years)	NR

									- no concomitant immunosuppressants (HR 1.4) - second-line anti-TNF (HR 1.32; CI 95% 1.01-1.69), - adalimumab vs.infliximab (HR 1.22) **Laboratory markers** - CRP per doubling (HR 1.04; CI 95% 1.00-1.08) - FC per doubling (HR 1.13; CI 95% 1.02-1.27)	

Specific data for CD is represented, unless stated otherwise.

aHR, adjusted Hazard Ratio; Anti-TNF, Anti-Tumour necrosis factor; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's disease endoscopic index of severity; CRP, C-reactive protein; EIM: extraintestinal manifestations; FC, faecal calprotectin; HBI, Harvey-Bradshaw Index; HR, hazard ratio (95% confidence interval); IBDU, inflammatory bowel disease unclassified; IMM, immunomodulator; IQR, interquartile range; MRE, magnetic resonance enterography; MRI, magnetic resonance imaging, NA, non-applicable; NR, non-reported; OR, odds ratio (95% confidence interval); RR, relative risk; SES-CD, simple endoscopic score in Crohn's disease; TL, trough level; UC, ulcerative colitis

Montreal classification: A1, < 16 years; A2, 17-40 years; B1, non-stricturing/non-penetrating; B2, stricturing; L1, ileal; L2, colonic; L3, ileocolonic; L4, isolated upper disease.

* Abstract form

** Anti-TNF de-escalation (included both studies that discontinued anti-TNF and studies that de-escalated the dose/interval)

*** Predictive factors were analysed in the retrospective observational study only, not in the meta-analysis

Appendix 4: Survey of research-active IBD clinicians around the UK

We recognise the huge impact of COVID on clinical IBD services. The COVID pandemic also appears to risk decimating current IBD research activity in the UK – with potentially significant consequences for some of our future treatment options.

We need your help to tell us about the impact on your hospital in a short 15 question survey, which should take no more than 5 minutes (thanks in advance for your time during this testing period). All results will be anonymised and analysed by number of sites surveyed. We want to finish this in 2 weeks and will share the results with you and the IBD research community in the UK.

Please place X next to the answer that fits what you are doing at your site. (Each question can also be accompanied by free text entry).

1. Can you provide a rough estimate of how many new patients were recruited to **academic interventional** IBD trials at your site over the last 12 months?
    a. <5
    b. 6-10
    c. 11-20
    d. 21-30
    e. >30

2. Can you provide a rough estimate of how many new patients were recruited to **commercial interventional** IBD trials at your site over the last 12 months?
    a. <5
    b. 6-10
    c. 11-20
    d. 21-30
    e. >30

3. Can you provide a rough estimate of how many new patients were recruited to **observational** IBD studies at your site over the last 12 months?
    a. <50
    b. 51-100
    c. 101-200
    d. 201-300
    e. >300

4. Are you still recruiting new patients to most **academic interventional** IBD trials at your site? (we recognise there may be many factors driving decisions for different trials, please select the option/options driving decisions locally within your unit for most trials in this category, place X next to all that apply)
    a. No, decision by local R&D team
    b. No, decision by local IBD team
    c. No, decision by trial sponsors
    d. Yes, with reduced recruitment
    e. Yes, with normal recruitment

5. Are you still recruiting new patients to most **commercial interventional** IBD trials at your site? (we recognise there may be many factors driving decisions for different trials, please select the option/options driving decisions locally within your unit for most trials in this category, place X next to all that apply)
    a. No, decision by local R&D team
    b. No, decision by local IBD team

c. No, decision by trial sponsors
d. Yes, with reduced recruitment
e. Yes, with normal recruitment

6. Are you still recruiting new patients to most **observational** IBD studies at your site? (we recognise there may be many factors driving decisions for different trials, please select the option/options driving decisions locally within your unit for most studies in this category, place X next to all that apply)
    a. No, decision by local R&D team
    b. No, decision by local IBD team
    c. No, decision by study sponsors
    d. Yes, with reduced recruitment
    e. Yes, with normal recruitment

7. For participants taking part in an IBD clinical trial, are you continuing protocolised trial visits?
    a. Stopped all research trial visits
    b. Continuing virtual research visits only
    c. Continuing mix of virtual and face-to-face research visits
    d. Continuing all face-to-face research visits currently

8. For participants taking part in an IBD clinical trial, are you still continuing protocolised trial procedures?
    a. Stopped all research imaging and endoscopy
    b. Continuing research endoscopy but no research imaging
    c. Continuing research imaging but no research endoscopy
    d. Continuing both research imaging and endoscopy on selected cases
    e. Continuing both research imaging and endoscopy as normal currently

9. For participants taking part in an IBD clinical trial, which of these would you consider critical trial data for ongoing collection? (can select multiple options, place X next to all that apply)
    a. Clinical data such as symptom severity scores
    b. Questionnaire data such as quality of life questionnaires
    c. Clinical blood tests such as CRP
    d. Clinical stool tests such as faecal calprotectin
    e. Research blood samples
    f. Research stool samples
    g. Research biopsy samples

10. For participants taking part in an IBD clinical trial at your site, which of these will you continue collecting as part of critical trial data collection? (can select multiple options, place X next to all that apply)
    a. Clinical data such as symptom severity scores
    b. Questionnaire data such as quality of life questionnaires
    c. Clinical blood tests such as CRP
    d. Clinical stool tests such as faecal calprotectin
    e. Research blood samples
    f. Research stool samples
    g. Research biopsy samples

11. What has been the impact on research staff allocation at your site? (can select multiple options, place X next to all that apply)

a. No reallocation of research personnel currently
b. Reallocation of some research nurses to clinical care
c. Reallocation of all research nurses to clinical care
d. Reallocation of some research fellows to clinical care
e. Reallocation of all research fellows to clinical care

12. Do you have a local process and personnel in place to allow identification and prompt serious adverse event reporting for patients in IBD trials who are hospitalised with COVID (within 24 hours of event)?
    a. Yes clear process and personnel in place to enable prompt SAE reporting
    b. Not yet in place, but developing process and personnel to enable prompt SAE reporting
    c. No clear process or personnel in place to enable prompt SAE reporting

13. Have there been any issues with medication supply for IBD trials at your site?
    a. No impact on delivery/supply of trial medication currently
    b. Minor impact on delivery/supply of trial medication
    c. Major impact on delivery/supply of trial medication

14. Have there been any issues with infusion services for IBD trials at your site?
    a. No impact on trial infusion services currently
    b. Some trial medication infusions halted
    c. All trial medication infusions halted

15. How best do you think the UK IBD research community can mitigate the impact of COVID and improve efficiency of IBD trials for the future?
    a. Virtual visits and/or consenting
    b. Home-based treatments
    c. Remote monitoring tests
    d. Active-treatment control arms in clinical trials
    e. Use of innovative trial designs such as platform trials

Appendix 5: Eligibility for late-phase MAMS protocols

Category	Inclusion criteria
Population	Humans
Interventions	No restrictions
Comparator	No restrictions
Outcomes	No restrictions
Study design	MAMS protocols defined as: • Multiple arm (2 or more actual or intended comparison arms) • Multiple stage (2 or more actual or intended stages with an interim analysis in between stages) • Interim analyses to assess for lack of benefit/insufficient activity and enable stopping to trial recruitment arms to go to next stage of trial +/- possibility to add in new trial arms • Phase 3 or seamless phase 2/3 or can be only phase 2 if intended and pre-planned for phase 3 expansion at outset • Randomised
Other	Peer-reviewed publications, conference abstracts, published protocols and trial registrations in the English language

Appendix 6: Search strategy used for publications and registrations

Search strategy MEDLINE/PubMed

Executed on December 31, 2022

No.	Terms	Hits	Comments
1	(Master protocol or master trial protocol or trial master protocol).mp.	14	Master protocol
2	(Platform trial or platform clinical trial or adaptive platform trial or platform adaptive trial).mp.	156	Platform trial design
3	(Adaptive trial or adaptive clinical trial).mp.	251	Adaptive trial design
4	(Multi-arm multi-stage or MAMS or two-arm multi-stage or TAMS).mp.	16	Multi-arm multi-stage design
5	(Bayesian clinical trial or bayesian adaptive).mp.	37	Adaptive
6	Phase 3 clinical trial or phase iii clinical trial	33789	Phase 3
7	Seamless phase 2 clinical trial or seamless phase ii clinical trial	101	Seamless phase 2
8	Or/1-5	474	Combine trials
9	Or/6-7	33890	Combine phases
10	And/8-9	258	Final results

Search strategy for CENTRAL

Executed on December 31, 2022

No.	Terms	Hits	Comments
1	(Master protocol or master trial protocol or trial master protocol).mp.	1400	Master protocol
2	(Platform trial or platform clinical trial or adaptive platform trial or platform adaptive trial).mp.	8973	Platform trial design
3	(Adaptive trial or adaptive clinical trial).mp.	6163	Adaptive trial design
4	(Multi-arm multi-stage or MAMS).mp.	78	Multi-arm multi-stage design
5	(two-arm multi-stage or TAMS).mp.	80	Two-arm multi-stage design
6	(Bayesian clinical trial or bayesian adaptive or Bayesian trial).mp.	1550	Adaptive
7	(Phase 3 or phase iii).mp.	68447	Phase 3
8	(Seamless 2-3 or seamless 2 to 3 or seamless 2/3 or seamless phase ii/iii or seamless phase 2/3).mp.	30	Seamless design
9	humans	591026	Limiting to studies on humans
10	Or/1-6	12948	Limiting to trials
11	Or/7-8	68461	Limited to late phase
12	And/9-11	162	Final results

Search strategy for ClinicalTrials.gov, ISRCTN registry, and EU Clinical Trials Register

Executed on December 31, 2022

Search details	URL
Clinicaltrials.gov	
Master protocol	https://clinicaltrials.gov/ct2/results?cond=&term=master+protocol&cntry=&state=&city=&dist=&Search=Search
Adaptive trial	https://clinicaltrials.gov/ct2/results?cond=&term=adaptive+trial&cntry=&state=&city=&dist=&Search=Search
Platform trial	https://clinicaltrials.gov/ct2/results?cond=&term=platform+trial&cntry=&state=&city=&dist=&Search=Search
Multi-arm multi-stage	https://clinicaltrials.gov/ct2/results?cond=&term=Multi-arm+multi-stage&cntry=&state=&city=&dist=&Search=Search
ISRCTN registry	
Master protocol	http://www.isrctn.com/search?q=master+protocol
Adaptive trial	http://www.isrctn.com/search?q=adaptive+trial
Platform trial	http://www.isrctn.com/search?q=platform+trial
Multi-arm multi-stage	http://www.isrctn.com/search?q=Multi-arm+multi-stage+trial
EU Clinical Trials Register	
Master protocol	https://www.clinicaltrialsregister.eu/ctr-search/search?query=master+protocol
Adaptive trial	https://www.clinicaltrialsregister.eu/ctr-search/search?query=adaptive+trial
Platform trial	https://www.clinicaltrialsregister.eu/ctr-search/search?query=platform+trial
Multi-arm multi-stage	https://www.clinicaltrialsregister.eu/ctr-search/search?query=multi-arm+multi-stage+trial
WHO ICTRP	
Master protocol/ platform trial/multi-arm multi-stage/phase 2/phase 3/phase 4	https://apps.who.int/trialsearch/AdvSearch.aspx

Appendix 7: Data extraction sheet for MAMS trial conduct

Conduct of MAMS protocols (complete one form per trial using MAMS protocol)			
Extractor's initials		Date form completed	
Trial name (short version/acronym)			
Sponsor organisation			
Clinical Trials Unit/Clinical Research Organisation involved	No ☐ Yes ☐ Unclear ☐ (If yes, give name):		
Phase of trial	Phase II with pre-specified option for phase III expansion ☐ Seamless phase II/III ☐ Phase III ☐ Other ☐ Describe:		
CI name		**Contact email(s)**	
ISRCTN number(s)		**NCT number(s)**	
EudraCT number(s)		**Other ID**	
Data extraction source(s)	Trial registry(ies) ☐ Publication(s) ☐ Trial website ☐ Contact with trial team ☐ Other ☐ If other, describe:		
Trial registry	WHO ICTRP ☐ Clinicaltrials.gov ☐ ISRCTN ☐ Other ☐ Describe:		
Trial registration	Single clinical trial registration with amendment for each comparison arm ☐ Separate clinical trial registration protocol for each comparison arm ☐ Unclear ☐		
	Source and quote:		
Trial recruitment overview	Not started recruitment yet ☐ Recruitment ongoing in some or all arms ☐ All arms completed recruitment and in trial follow-up for primary outcome measure ☐ All arms completed trial scheduled follow-up for primary outcome measure ☐ Unclear ☐		
	Source and quote:		
Source(s) of funding	Academic ☐ Industry ☐ Charity ☐ Other ☐ Describe:		
Country of the overall co-ordinating site/unit/organisation			
	Source and quote:		
Number of countries patients being recruited from			
	Source and quote:		

Number of randomisations performed per patient	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 6+ ☐ Unclear ☐		
	Source and quote:		
Masking of treatment allocation	Open ☐ Patients only ☐ Researchers only ☐ Double-blind ☐ Unclear ☐		
	Source and quote:		
Interventions under investigation	CTIMP ☐ Non-CTIMP surgical ☐ Non-CTIMP non-surgical ☐ Unclear ☐		
Population (e.g. adults with diabetes)			
Opening date and accrual date	Date trial open to recruitment (N/A if not applicable):	Date of first patient accrual (N/A if not applicable):	
Anticipated and actual recruitment of participants	Target recruitment for overall trial:	Actual recruitment to date for overall trial:	
	Source and quote:		
Anticipated and actual recruitment of participants by comparison arm (if applicable)	Comparison arm:	Target recruitment:	Actual recruitment:
	Source and quote:		
Number of comparison arms when trial opened	2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 7+ ☐ Unclear ☐		
	Source and quote:		
Maximum number of comparison arms pre-planned	2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 7+ ☐ Unclear ☐		
	Source and quote:		
Total number of comparison arms investigated to date	2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 7+ ☐ Unclear ☐		
	Source and quote:		

Shared control arm	Contemporary ☐ Historical ☐ Unclear ☐ No ☐		
Comparison arms which have published primary results	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 5+ ☐ Unclear ☐		
	Source and quote:		
Comparison arms which have recruited but not published primary results	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 5+ ☐ Unclear ☐		
	Source and quote:		
Number of comparison arms stopped early	0 ☐ 1 ☐ 2 ☒ 3 ☐ 4 ☐ 5 ☐ 5+ ☐ Unclear ☐		
	Source and quote:		
Intervention arm(s) no longer recruiting (can be multiple)	Stopped recruitment early for poor recruitment ☐ Stopped recruitment early following interim analysis recommendation ☐ Completed anticipated recruitment ☐ Unclear ☐ Not applicable ☐		
	Source and quote for each arm no longer recruiting:		
Definitive primary outcome(s)		Clinical ☐ Methodological/other ☐	
Interim outcome measure(s)		Clinical ☐ Methodological/other ☐	
Number of stages with interim analyses in between for each comparison (defined as ability to stop recruitment to arms at interim)	Comparison arm:	Planned number of stages:	Number of stages to date:
	Source and quote:		

Frequency of interim analyses	After a set number of events in the control arm ☐ After a set period of time ☐ After a set number of participants recruited ☐ Other ☐ If other, describe: Unclear ☐
	Source and quote:
Method for stopping recruitment to/selecting intervention arms	Lack of benefit hurdles (keep on relative merit) ☐ Dropping set number of arms at each stage ☐ Drop-the-losers/keep-the-winner design ☐ Unclear ☐ Other ☐ (If other, describe):
Software used to determine sample size calculations	
	Source and quote:
Is there strong control of family-wise error rate	No ☐ Yes ☐ Unclear ☐ (If yes, describe):
	Source and quote:
Repurposed drugs as intervention arms	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 5+ ☐ Unclear ☐
Biomarker discovery or incorporation	Prognostic ☐ Predictive response ☐ Predictive side effects ☐ None ☐ Unclear ☐
Master protocol format	Single protocol for all comparison arms ☐ Master protocol with separate sub-protocol for each comparison arm ☐ Separate clinical trial protocol for each comparison arm ☐ Unclear ☐ Other ☐ (If other, describe):
	Source and quote:
Access to protocol	Open-access ☐ Closed-access provided on request ☐ Closed-access not provided on request ☐ Closed-access no response to request ☐
Protocol paper(s) published	No ☐ Yes ☐ In press ☐ Unclear ☐
	Source:
Reporting paper(s) published	No ☐ Yes ☐ In press ☐ Unclear ☐
	Source:
Methodology paper(s) published	No ☐ Yes ☐ In press ☐ Unclear ☐
	Source:
Editorial paper(s) or news items published	No ☐ Yes ☐ In press ☐ Unclear ☐
	Source:

Any reference to financial savings in protocol/publications /news items	No ☐	Yes ☐	Unclear ☐	
	Source and quote:			
Any reference to efficiency savings in protocol/publications /news items	No ☐	Yes ☐	Unclear ☐	
	Source and quote:			
Any reference to perpetual/ eternal trial in protocol/publications /news items	No ☐	Yes ☐	Unclear ☐	
	Source and quote:			
Any reference to MRC CTU MAMS papers in trial protocol or publications	No ☐	Yes ☐	Unclear ☐	Not applicable ☐
	Source and quote:			
MRC CTU individual(s) and input into trial	Co-ordinated from MRC CTU ☐ Help with design/consultation ☐ Member of Trial Management Group ☐ Member of Trial Steering Committee ☐ Member of independent Data Monitoring Committee ☐ No direct involvement ☐			
Citation/mention of nstage module in any trial documents or publications	Yes direct citation/mention of nstage ☐ Yes indirect citation/mention of nstage via STATA ☐ No citation/mention of nstage ☐			
Page length of patient information sheet (PIS) for overall trial	1 ☐	2 ☐	3 ☐	4 ☐
	5 ☐	6 ☐	6+ ☐	Unclear ☐
Page length of PIS for individual arms (can be multiple)	1 ☐	2 ☐	3 ☐	4 ☐
	5 ☐	6 ☐	6+ ☐	Not applicable ☐
	Source and quote:			
Number of languages available for PIS for overall trial	1 ☐	2 ☐	3 ☐	4 ☐
	5 ☐	6 ☐	6+ ☐	Not applicable ☐
	Source and quote:			
Number of languages for PIS of individual arms (can be multiple)	1 ☐	2 ☐	3 ☐	4 ☐
	5 ☐	6 ☐	6+ ☐	Not applicable ☐
	Source and quote:			

Additional patient information media	Video ☐ Audio ☐ Mobile app ☐ Other ☐ None ☐ (If other, describe):
Patient consent process for trial	One-off process ☐ Staged process ☐ Unclear ☐
Stages of patient and public involvement/ partnership	Prior to obtaining funding ☐ During trial setup ☐ During trial conduct ☐ During trial analysis ☐ During trial dissemination ☐ Unclear ☐ None ☐
Patient and public member(s)	Trial management group (TMG) ☐ Trial steering group (TSC if applicable) ☐ Data monitoring committee (DMC) ☐ Unclear ☐ None ☐
Time from funding to trial opening (months)	
	Source and quote:
Case report forms for trial data collection	Core case report forms with a few additional forms for each intervention ☐ Entirely new and separate case report forms for each intervention ☐ Unclear ☐
How many separate databases during trial	1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 6+ ☐ Unclear ☐
Which database(s) used for trial	
iDMC oversight	One committee for whole trial ☐ One committee for each intervention arm ☐ Combination of separate committees for trial and intervention arms ☐ Umbrella DMC overseeing many similar trials ☐ Unclear ☐
Number iDMC members for overall trial	2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 7+ ☐ Unclear ☐
Average number iDMC members if have separate iDMCs for individual arms	2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 7+ ☐ Unclear ☐ Not applicable ☐
Any DMC clinicians with previous MAMS experience	No ☐ Yes ☐ Unclear ☐ (If yes, describe):
	Source and quote:
Any DMC statisticians with previous MAMS experience	No ☐ Yes ☐ Unclear ☐ (If yes, describe):
	Source and quote:

Regulatory agency inspecting overall trial	MHRA ☐ EMA ☐ FDA ☐ Other ☐ Unclear ☐
	Source and quote:
Requirements for trial closure specified	No ☐ Yes ☐ Unclear ☐ (If yes, describe):
	Source and quote:
Largest barrier reported to delivery or conduct of this MAMS protocol by trial team	Funding ☐ Site set-up ☐ Recruitment ☐ Retention ☐ Follow-up ☐ Regulation ☐ Monitoring ☐ Interim analysis ☐ Other ☐ (If other, describe): None ☐
	Source and quote:
Would you as trial team classify this as a MAMS trial	No ☐ Yes ☐ Other ☐ (Describe):

Appendix 8: DMC survey for trialists

Survey on Novel Trial Designs and Data Monitoring Committees for Randomised, Late-Phase Clinical Trials

We are conducting a global survey of data monitoring committee practices in randomised, late-phase clinical trials. We are a group of researchers, doctors, patients and public individuals from the United Kingdom involved in clinical trials being undertaken in many parts of the world. We also have a particular interest in the use of more novel trial designs and platforms.

We understand that there are significant differences for data monitoring committees between academic trials (non-commercial) and industry (commercial trials). For the purposes of this survey, this relates to the sponsor of the trial and whether they are an academic (non-commercial) or industry (commercial) sponsor.

This work is being completed as part of a PhD on improving clinical trials by Nuru Noor (a PhD student at the MRC Clinical Trials Unit based at University College London).

This survey is voluntary and has seven short sections (sections A-G) which take about 15-20 minutes to complete. This survey can be completed anytime until 30 November 2019 but should only be completed once by any one person.

As an incentive, we are able to offer ten vouchers worth £50 (or equivalent) to those who complete the survey and provide a contact email address at the end. These individuals will be selected at random and notified of their prize.

All findings from this survey will be anonymised and then analysed, so no comments will be attributed to any individual or organisation.

We will publish findings of this survey. If you would like to be notified when this happens, please provide your email address at the end of the survey – there is an option for you to do this. All data from this survey will conform to the NHS Digital Information Governance toolkit and security standards.

We are grateful for your time and responses. If you have any queries then please feel free to contact: nurulamin.noor.18@ucl.ac.uk.

I confirm that I have read and understood the information about this survey and what is expected of me. By clicking next, I agree to take part in this survey.

Glossary of terms

Trial Management Group (TMG)

A trial management or executive group (or similarly named) that is responsible for the day-to-day conduct and running of a clinical trial. The TMG usually includes researchers who had the initial idea and gained funding for the trial. They work with representatives from different areas involved in the trial including doctors, nurses, statisticians, trial and data managers and PPI individuals.

Data Monitoring Committee (DMC)

A data monitoring committee (or similarly named) would commonly be composed of individuals who are independent of the trial. Their role is to review trial data (usually not blinded to the allocation) as the trial progresses, and to make recommendations to the trial steering committee/trial management group based on these findings about what should happen in the trial, mainly in terms of whether it should continue or stop or be amended.

These committees are given many different names and acronyms including; data monitoring committee (DMC), independent data monitoring committee (IDMC), data monitoring and ethics committee (DMEC), data safety and monitoring board (DSMB) and other similar named groups. For the purposes of this survey, we have used data monitoring committee (DMC) to cover all of these terms.

Trial Steering Committee (TSC)

A trial steering committee (or similarly named) is composed of individuals, some of whom are members of the trial management group and some of whom are independent of the trial. Their role is to provide overall executive oversight and make recommendations about key decisions and conduct to the sponsor of a clinical trial. A TSC may not be common in some parts of the world, where some of these roles may either be performed by a TMG or DMC.

Research Ethics Committee (REC)

A research ethics committee is a group composed of individuals who review clinical trial research applications and give an opinion about whether it is ethical to proceed with the research. These committees aim to ensure research is conducted to meet ethical standards and is of scientific merit. These committees are given many different names and acronyms including; research ethics committee (REC), institutional review board (IRB) and other similar named groups. For the purposes of this survey, we have used the term research ethics committee (REC) throughout.

Section A – Background (a few questions about yourself)

This is a survey about data monitoring committee practices in late-phase, randomised clinical trials. This section focuses on your individual background in clinical trials.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

1. Which country are you primarily based in for work?
    a. Dropdown list of countries

2. Which age group are you currently in?
    a. <20 years old
    b. 21-30 years old
    c. 31-40 years old
    d. 41-50 years old
    e. 51-60 years old
    f. 61+ years old

3. What is your primary working role in/engagement with late-phase, randomised, clinical trials?
    a. Statistician
    b. Chief Investigator (select if current role as chief investigator for a late-phase, randomised, clinical trial)
    c. Principal/site investigator predominantly in hospital setting
    d. Principal/site investigator predominantly in industry setting
    e. Clinician predominantly in academic clinical trials unit
    f. Trial co-ordinator (descriptor sentence)
    g. Data manager (descriptor sentence)
    h. Pharmacist
    i. Other (please describe)

4. How many years' experience do you have in **late-phase, randomised,** clinical trials (to nearest figure)? (matrix for industry vs academia)
    a. 0 years
    b. 1-2 years
    c. 3-5 years
    d. 6-10 years
    e. 10+ years

5. How many **late-phase, randomised, clinical** trials have you helped co-ordinate or been part of the trial management group? (matrix for industry vs academia)
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. 10+

6. How many **early-phase or non-randomised, clinical** trials have you helped co-ordinate or been part of the trial management group? (matrix for industry vs academia)
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. 10+

7. What is the predominant disease area for the clinical trials you have been part of the trial management group? (if experience in multiple areas, please select the predominant area)
    a. Cancer
    b. Infection (e.g. HIV, tuberculosis)
    c. Neurological (e.g. Parkinson's disease, Alzheimer's dementia)
    d. Cardiovascular (e.g. heart disease, stroke)
    e. Inflammatory (e.g. asthma, Crohn's disease)
    f. Other (please describe)

Section B – Novel trial designs and platform approaches

This section focuses on more novel trial designs and platform approaches. Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

Even if you have not been directly involved in late-phase clinical trials or only have limited experience of late-phase clinical trials, we would still highly value your opinion and responses to questions below.

1. Of the late-phase, randomised trials you have been involved in, approximately how many have used platform protocols for the trial (a platform protocol typically addresses multiple primary hypotheses in a clinical trial)? (matrix for industry vs academia)
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. 10+

2. How confident would you be on being a member of a trial management group for a late-phase, randomised trial using a platform protocol to address multiple primary research hypotheses?
    a. Very low confidence
    b. Low confidence
    c. Fair confidence
    d. High confidence
    e. Very high confidence

3. Separately to trials using a platform protocol, of the late-phase, randomised trials you have been involved in, approximately how many have used a biomarker-incorporating approach? (matrix for industry vs academia)
    a. 0
    b. 1-2
    c. 3-5
    d. 6-10
    e. 10+

4. How confident would you feel on being a member for a trial management group for a late-phase, randomised, clinical trial using a biomarker-incorporating approach?
    a. Very low confidence
    b. Low confidence
    c. Fair confidence
    d. High confidence
    e. Very high confidence

Section C – DMC experiences

This section will now focus on independent data monitoring committees (DMCs). The names used for DMCs can vary between individual trials and countries. This section has a combination of questions exploring details of your interaction with DMCs, how DMCs function in a clinical trial, as well as seeking your opinion on the optimal role of DMCs.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

1. How many years' experience do you have **reporting to** a DMC in late-phase, randomised, clinical trials? (matrix for industry vs academia)
    a. 0
    b. 1-2 years
    c. 3-5 years
    d. 6-10 years
    e. 10+ years

2. How many years' experience do you have **being an** independent member of a DMC in late-phase, randomised clinical trials? (matrix for industry vs academia)
    a. 0
    b. 1-2 years
    c. 3-5 years
    d. 6-10 years
    e. 10+ years

3. For late-phase, randomised, clinical trials you have been involved in, are DMC members routinely named in the trial protocol? (matrix for industry vs academia)
    a. Never
    b. Hardly ever
    c. Often
    d. Yes always
    e. Unknown
    f. Not applicable

4. For late-phase, randomised, clinical trials you have been involved in, are DMC members routinely acknowledged in the **published protocol paper (trial protocol manuscript)**? (matrix for industry vs academia)
    a. Not acknowledged
    b. Named in factual list on manuscript
    c. Acknowledged in manuscript
    d. Named co-author of manuscript
    e. Not applicable

5. For late-phase, randomised, clinical trials you have been involved in, are DMC members routinely acknowledged in the published **main/final results paper (trial reporting manuscript)**? (matrix for industry vs academia)
    a. Not acknowledged
    b. Named in factual list on manuscript
    c. Acknowledged in manuscript
    d. Named co-author of manuscript
    e. Not applicable

6. Have **you personally** accepted an honorarium/payment for being an independent member of a DMC for a late-phase clinical trial? (matrix for industry vs academia)

a. Never been offered
b. Offered and always decline
c. Offered and usually decline
d. Offered and usually accept
e. Not been a member of a DMC

7. For late-phase clinical trials you have been involved in, have the **other DMC members** usually been offered an honorarium/payment for their role? (matrix for industry vs academia)
    a. Never been offered honorarium/payment
    b. Usually offered but declined honorarium/payment
    c. Usually offered and accept honorarium/payment
    d. Unknown
    e. Not applicable

Section D – Roles of the DMC

This section will now focus on the role of data monitoring committees (DMCs) in late-phase, randomised clinical trials.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

16. Should trial statistical analysis plans routinely be reviewed by the DMC prior to being signed off? (matrix for industry vs academia)
    f. No
    g. Yes
    h. Other (please describe)

17. Should final trial reporting manuscripts (results paper) be reviewed by the DMC prior to submission? (matrix for industry vs academia)
    a. No
    b. Yes
    c. Other (please describe)

18. Should the DMC have a role in determining additional analyses to the main report? (matrix for industry vs academia)
    a. No
    b. Yes
    c. Other (please describe)

19. Should the DMC have a role in sharing of clinical trial results? (matrix for industry vs academia)
    a. No
    b. Yes before primary results available
    c. Yes before and after primary results available
    d. Other (please describe)

20. In your local organisation, do you have a process for selecting DMC members for clinical trials? (matrix for industry vs academia)
    a. No
    b. Yes
    c. Unknown

21. Who do you think should be responsible for selecting DMC members? (can select multiple options) (matrix for industry vs academia)
    a. Trial funders

b. Trial sponsors
c. Trial statistician
d. Trial co-ordinator
e. Chief Investigator
f. Director of trials unit/organisation

Section E – Experience required by a DMC

This section will now focus on the experiences required to fulfil role as member of data monitoring committees (DMCs) in late-phase, randomised clinical trials.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

1. What experience do you think DMC members should have to be adequately prepared for a DMC role? (matrix for industry vs academia)
    a. Published widely in field
    b. Previous role on TMGs
    c. Previous role on TSCs
    d. Previous role on DMCs
    e. Other

2. Have you ever experienced any difficulties caused by inexperienced DMC members?
    a. No
    b. Yes
    c. Not applicable

3. How difficult do you find recruiting members with appropriate **clinical experience** for DMCs? (matrix for industry vs academia)
    a. Easy
    b. Varies depending on disease area
    c. Varies depending on trial design/platform
    d. I have not had to look yet
    e. Not my responsibility
    f. Difficult

4. How difficult do you find recruiting members with appropriate **statistical experience** for DMCs? (matrix for industry vs academia)
    a. Easy
    b. Varies depending on disease area
    c. Varies depending on trial design/platform
    d. I have not had to look yet
    e. Not my responsibility
    f. Difficult

5. How do you think implementing more novel trial designs or platform approaches influence the ability to find suitable independent DMC members for late-phase, randomised clinical trials? (matrix for industry vs academia)
    a. Easier
    b. The same
    c. More difficult
    d. Unknown

Section F – PPI and DMCs (penultimate section)

This section will now focus on patient and public involvement (PPI) and data monitoring committees (DMCs) in late-phase, randomised clinical trials.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

1. Approximately how many trials to closest percentage have you been involved in with a DMC member that would be considered a PPI representative for a late-phase, randomised trial? (to closest approximate figure) (matrix for industry vs academia)
    a. 0%
    b. 25%
    c. 50%
    d. 75%
    e. 100%

2. Given your response to previous question and involvement in a trial where the DMC has included a PPI member, please highlight their background? (matrix for industry vs academia)
    a. Patient with condition under investigation not participating in the trial
    b. Patient support group/charity representative
    c. Lay public representative
    d. Unknown
    e. Other (please describe)

3. Have you or your organisation considered having PPI representatives as independent members of DMCs? (matrix for industry vs academia)
    a. No, never considered and not worth exploring in future
    b. No, never considered but worth exploring in future
    c. Yes, considered but decided not to do so in near future
    d. Yes, actively pursuing this for current/future trials

4. When do you think having a PPI member on a DMC could be beneficial? (matrix for industry vs academia)
    a. Never beneficial
    b. Not convinced currently but would re-consider if see evidence of benefit
    c. I am not sure
    d. Potentially beneficial depending on the type of trial
    e. Always beneficial, should be the case for every trial

5. Do you think that any of these trial population factors would increase the need for a PPI individual as an independent member of a DMC? (can select multiple options) (matrix for industry vs academia)
    a. Acute condition (e.g. flu virus)
    b. Progressive condition (e.g. dementia)
    c. Chronic condition (e.g. asthma)
    d. Life-threatening condition (e.g. heart attack)
    e. Rare condition (e.g. sarcoma cancer)

6. Do you think that any of these trial outcome factors would increase the need for a PPI individual as an independent member of a DMC? (can select multiple options) (matrix for industry vs academia)
    a. Subjective outcome measure (e.g. patient self-reported outcome)
    b. Objective outcome measure (e.g. blood test marker of inflammation)

7. Do you think that any of these trial designs or platform approaches would increase the need a PPI individual as an independent member of a DMC? (can select multiple options) (matrix for industry vs academia)
    a. Biomarker/stratified medicine designs
    b. Adaptive designs
    c. Platform protocols
    d. Protocols that will add intervention arms
    e. Protocols active for <5 years
    f. Protocols active for >10 years

8. If there were to be an independent PPI member of a DMC, which of the following would help best recognise their contribution? (can select multiple options) (matrix for industry vs academia)
    a. Reimbursement of expenses incurred for role
    b. Payment/honorarium for role
    c. Offer of acknowledgement on trial manuscript
    d. Other (please describe)

Section G – Experience of DMC (final section)

This section is only to be completed by those with experience of being a member of a data monitoring committees (DMCs) in late-phase, randomised clinical trials.

If you have not been a member of a DMC, then you will be directed to the end of the survey.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

1. Have you even been an independent member of a DMC for late-phase clinical trials? (matrix for industry vs academia)
    a. No
    b. Yes

2. How many late-phase clinical trials have you been an independent member of a DMC? (matrix for industry vs academia)
    a. 1
    b. 2-5
    c. 5-10
    d. 10+

3. Of these DMCs you have been involved in, approximately how many late-phase, randomised clinical trials have used an adaptive trial design? (to closest approximate figure) (matrix for industry vs academia)
    a. 0%
    b. 25%
    c. 50%
    d. 75%
    e. 100%

4. Of these DMCs you have been involved in, approximately how many late-phase, randomised clinical trials have used a biomarker-incorporating approach? (to closest approximate figure) (matrix for industry vs academia)
    a. 0%
    b. 25%
    c. 50%
    d. 75%
    e. 100%

5. Of these DMCs you have been involved in, when was the first DMC meeting routinely held? (matrix for industry vs academia)
    a. Before recruitment starts
    b. After first patient recruited
    c. Following a set number/percentage of patients recruited
    d. Following a set number of months after trial opening
    e. Other (please describe)

6. Of these DMCs you have been involved in, how many have provided the DMC a chance to review the statistical plan before the first interim analysis? (to closest approximate figure) (matrix for industry vs academia)
    a. 0%
    b. 25%
    c. 50%
    d. 75%
    e. 100%

7. In late-phase, randomised clinical trials where you have been an independent member of the DMC, were formal stopping/decision rules established? (matrix for industry vs academia)
    a. Never
    b. Hardly ever
    c. Often
    d. Always
    e. Not applicable

8. A DMC may make recommendations to stop a trial early for a number of reasons. Which of these following terms would you feel comfortable understanding and knowing when to apply these recommendations?
    a. Stopping for harm (N/Y)
    b. Stopping for efficacy (N/Y)
    c. Stopping for futility (N/Y)

9. How comfortable do you feel when presented with results from stopping/decision rules such as Haybittle-Peto, Pocock, O'Brien-Fleming, Lan-DeMets, and how they work?
    a. Low confidence
    b. Moderate confidence
    c. High confidence

10. When is the **latest point** at which formal stopping/decision rules should be formalised for a trial? (matrix of industry vs academia)
    a. Before the trial starts
    b. Before recruitment starts
    c. Before the first DMC meeting
    d. Before statistical analysis plan finalised
    e. Other (please describe)

11. How do you think formal stopping/decision rules should be best used? (matrix of industry vs academia)
    a. As a formal basis to direct DMC decisions
    b. As a general guide to direct DMC decisions

12. Have you have been involved in a trial where a formal stopping rule requirement was met at an interim analysis but the trial still carried on? (matrix of industry vs academia)
    a. Yes continued through, despite early signs of potential efficacy
    b. Yes continued through, despite early signs of potential futility/lack of efficacy
    c. Yes continued through, despite early signs of potential harm
    d. Yes continued through, but unsure of reasons why
    e. Not applicable

Do you think this was an appropriate decision? (Additional free text comments)

13. Would you personally accept an invitation to join a future DMC as an independent member? (matrix for industry vs academia)
    a. Would not be member of DMC in the future
    b. Would only consider a DMC role if financial payment
    c. Would only consider a DMC role if academic interest in trial
    d. Would routinely be member of DMC in the future

14. Please provide your email address if you would be willing to be contacted about participating in a qualitative interview about experiences of being a DMC member? (leave blank if you do not want to be contacted further)

15. Please provide your email address if you would like to be notified when results of this survey have been analysed and published and to be entered for the prize draw for a gift voucher. (leave blank if you do not want to be notified)

Thank you for completing the survey.

The information you have given will be used to form a plain English summary which we hope can be used to improve practices of clinical trials in your country and others around the world.

If you have additional questions about this survey, please email nurulamin.noor.18@ucl.ac.uk

Appendix 9: DMC survey for PPI individuals

Survey of Patient and Public Involvement on Data Monitoring Committees

We are performing a global survey of patient and public involvement (PPI) in clinical trials where patients are given different treatments (randomised clinical trials).

We are a group of researchers, doctors, patients and public individuals from the United Kingdom involved in clinical trials around the world. We feel that it is very important for patients and the public to have the opportunity to be involved in such clinical trials.

During this survey we have used the term 'patient and public involvement' but we recognise that many other terms are used around the world, including involvement from community members, lay members, Experts by experience and many more terms. For this survey we have used the term PPI throughout. We also consider PPI being carried out 'with' or 'by' members rather than 'to', 'about' or 'for' them.

This work is being completed as part of a PhD on improving clinical trials by Nuru Noor (a PhD student at the MRC Clinical Trials Unit based at University College London). With the overall aim that this work informs future guidance on the topic and potential training/development opportunities if the findings of this survey are consistent with requirement for this.

This survey is voluntary and takes about 10 minutes to complete. There are 19 multiple choice questions and four questions about you. This survey can be completed anytime until 30 April 2020 but should only be completed once by any one person.

As an incentive, we are able to offer ten vouchers worth £50 each (or the global equivalent) to those who complete the survey and provide a contact email address at the end. These individuals will be selected at random and notified of their prize.

Please click next to move to the next page, where you can find out more about the survey and then you can either agree or decline to take part in this survey.

Open and closed questions will be used throughout this survey to understand about your experiences and opinions of clinical trials. All findings from this survey will be anonymised and then analysed, so no comments will be attributed to any individual or organisation.

We will publish findings of this survey. If you would like to be notified when this happens, please provide your email address at the end of the survey – there is an option for you to do this.

We are committed to protecting and respecting your privacy. All data from this survey will conform to the United Kingdom National Health Service (NHS) Digital Information Governance toolkit and security standards.

If personal data such as email address is provided at the end of this survey, then this will not be shared with any outside providers and will be processed in a GDPR compliant manner and conform to NHS Digital's Information Governance Toolkit. All information will also conform to the UCL general research participant privacy notice, which can be found by clicking on the following link.

We are grateful for your time and responses. If you have any queries then please feel free to contact: nurulamin.noor.18@ucl.ac.uk. If you wish to raise a complaint about this work then please contact ethics@ucl.ac.uk.

I confirm that I have read and understood the information about this survey and what is expected of me. By clicking next, I agree to take part in this survey.

Glossary of terms to start

Trial Management Group (TMG)

A trial management or executive group (or similarly named) that is responsible for the day-to-day conduct and running of a clinical trial. The TMG usually includes researchers who had the initial idea and gained funding for the trial. They work with representatives from different areas involved in the trial including doctors, nurses, statisticians, trial and data managers and PPI individuals.

Trial Steering Committee (TSC)

A trial steering committee (or similarly named) is composed of individuals, some of whom are members of the trial management group and some of whom are independent of the trial. Their role is to provide overall executive oversight and make recommendations about key decisions and conduct to the sponsor of a clinical trial.

Data Monitoring Committee (DMC)

A data monitoring committee (or similarly named) would commonly be composed of individuals who are independent of the trial. Their role is to review trial data (usually not blinded to the allocation) as the trial progresses, and to make recommendations to the trial steering committee/trial management group based on these findings about what should happen in the trial, mainly in terms of whether it should continue or stop or be amended.

These committees are given many different names and acronyms including; data monitoring committee (DMC), independent data monitoring committee (IDMC), data monitoring and ethics committee (DMEC), data safety and monitoring board (DSMB) and other similar named groups. For the purposes of this survey, we have used data monitoring committee (DMC) to cover all of these terms.

Research Ethics Committee (REC)

A research ethics committee is a group composed of individuals who review clinical trial research applications and give an opinion about whether it is ethical to proceed with the research. These committees aim to ensure research is conducted to meet ethical standards and is of scientific merit. These committees are given many different names and acronyms including; research ethics committee (REC), institutional review board (IRB) and other similar named groups. For the purposes of this survey, we have used the term research ethics committee (REC) throughout.

Please note that some questions allow multiple options to be selected whereas other questions ask for the nearest answer to reflect your views and experience.

Even if you have never been a member of a DMC or only have limited previous interaction with a DMC, we would still highly value your opinion and responses to the questions below.

1. Which of these statements best describes your background of PPI in clinical trials? (can select multiple options)
    a. I am a patient with who has taken part in clinical trial(s)
    b. I am a carer of a patient who has taken part in clinical trial(s)
    c. I am a family member of a patient who has taken part in clinical trial(s)
    d. I am member of staff for a patient support group/treatment advocacy group/charity which supports clinical trials
    e. Other (Please specify)

2. How many years' experience do you have of involvement (in any way) with clinical trials? (to nearest figure)
    a. <2 years
    b. 2-5 years
    c. 6-9 years
    d. 10+ years

3. What is the predominant area of the clinical trials for which you have been involved within? (if experience in multiple areas of clinical trials, please select the predominant area)
    a. Cancer
    b. Infection (e.g. HIV, tuberculosis)
    c. Neurological (e.g. Parkinson's disease, Alzheimer's dementia)
    d. Cardiovascular (e.g. heart disease, stroke)
    e. Inflammatory (e.g. asthma, Crohn's disease)
    f. Other (Please specify)

4. Have you ever been/or are you currently a member of the following? (can select multiple options)
    a. Member of trial management group
    b. Member of trial steering committee
    c. Member of research ethics committee
    d. Member of a research prioritisation committee e.g. clinical study groups which exist in some countries such as the United Kingdom
    e. None of the above

5. For how many clinical trials have you been an independent member of a data monitoring committee?
    f. 0
    g. 1
    h. 2-5
    i. 6-9
    j. 10+

6. A DMC may make recommendations to stop a trial early for a number of reasons. Regardless of previous involvement in a DMC, would you be comfortable understanding the following terms and knowing when to apply these recommendations?
    a. Stopping for harm (Do not understand/Understand)

b. Stopping for efficacy (Do not understand/Understand)
c. Stopping for futility (Do not understand/Understand)

7. How do you think formal stopping guidelines/rules (e.g. Haybittle-Peto, Pocock, O'Brien-Fleming, Lan-DeMets) should be best used in clinical trials?
    a. I do not feel adequately informed to answer this question
    b. As a general guide to direct DMC decisions
    c. As a formal basis to direct DMC decisions
    d. Other (Please specify)

8. What committee experiences do you think best prepare PPI individuals to be an independent member of a DMC? (can select multiple options)
    d. I do not feel adequately informed to answer this question
    e. Previous role on research ethics committee
    f. Previous role on trial management group
    g. Previous role on trial steering committee
    h. Previous role on data monitoring committee
    i. Other (Please specify)

9. How many DMCs would you expect a PPI individual to be an independent member of before they can be an effective member of the DMC?
    a. I do not feel adequately informed to answer this question
    b. 0
    c. 1
    d. 2-5
    e. 6-9
    f. 10+
    g. Other (Please specify)

10. To become an effective independent member of a DMC, how do you think the experience required for PPI members compares to clinicians/statisticians?
    a. I do not feel adequately informed to answer this question
    b. Less experience required for PPI members
    c. About the same experience required for PPI members
    d. More experience required for PPI members

11. When do you think having a PPI member on a DMC could be beneficial?
    f. Never beneficial
    g. Not convinced currently but would re-consider if see evidence of benefit
    h. I am not sure if would be beneficial or not
    i. Potentially beneficial depending on the type of clinical trial
    j. Always beneficial, should be the case for every clinical trial

12. Do you think that any of these trial population factors would increase the need for a PPI member on DMCs? (can select multiple options)
    a. I do not feel adequately informed to answer this question
    b. Acute condition (e.g. flu virus)
    c. Progressive condition (e.g. dementia)
    d. Chronic condition (e.g. asthma)
    e. Life-threatening condition (e.g. heart attack)
    f. Rare condition (e.g. sarcoma cancer)
    g. Other (Please specify)

13. Do you think that any of these trial outcome factors would increase the need for a PPI member on DMCs? (can select multiple options)

a. I do not feel adequately informed to answer this question
b. Subjective outcome measure (e.g. patient self-reported outcome)
c. Objective outcome measure (e.g. blood test marker of inflammation)
d. Other (Please specify)

14. Do you think that any of the following trial designs or approaches would increase the need for a PPI member on DMCs? (can select multiple options)
    a. I do not feel adequately informed to answer this question
    b. Biomarker/ stratified medicine designs (a marker such as blood test or genetic mutation used to guide treatment selection)
    c. Platform protocols (more than one primary research question)
    d. Protocols that will add intervention arms (as the trial progresses, new treatments may become available and get incorporated into the trial)
    e. Protocols active for >10 years
    f. Protocols active for <5 years
    g. Other (Please specify)

15. Which individuals would be the more suitable PPI members of a clinical trial DMC? (can select multiple options)
    a. I do not feel adequately informed to answer this question
    b. Patient with the condition being researched in a clinical trial
    c. Patient with different condition than the one being researched in a clinical trial
    d. Patient support group/charity representative from clinical area being researched in a clinical trial
    e. Patient support group/charity representative from different clinical area than the one being researched in a clinical trial
    f. Member of public with no experience of the condition being researched
    g. Other (Please specify)

16. If there were to be an independent PPI member of a DMC, which of the following would help best recognise their contribution? (can select multiple options)
    e. Reimbursement of expenses incurred for role
    f. Payment/honorarium for role
    g. Offer of acknowledgement on trial manuscript
    h. Other (Please specify)

17. Do you feel that PPI individuals would routinely want to be independent members of DMCs?
    a. No, this role is too complex for most PPI individuals
    b. Maybe, but only if sufficient training was provided
    c. Maybe, but only if they have sufficient experience of the research area
    d. Yes
    e. Other (Please specify)

18. Would you personally accept an invitation to join a DMC as an independent PPI member?
    a. Never
    b. Unlikely, I feel this role is too complex
    c. Yes, I would consider but only if sufficient training was provided
    d. Yes, I would definitely accept if I was interested in the trial
    e. Other (Please specify)

19. What training would be helpful to allow PPI individuals to fulfil their role as an independent PPI member on the DMC? (can select multiple options)

i. No specific training required
j. Specific guidelines for PPI members of a DMC
k. Observation of DMC meetings for a clinical trial
l. Mentoring by a member of DMC for a current clinical trial
m. Specific online statistical/clinical trial training course on DMCs
n. Specific face-to-face statistical/clinical trial training course on DMCs
o. Other (Please specify)

20. Which country are you primarily based in?
    a. Dropdown list of countries

21. Which age group are you currently in?
    b. <20 years old
    c. 21-30 years old
    d. 31-40 years old
    e. 41-50 years old
    f. 51-60 years old
    g. 61+ years old

22. Please provide your email address if you would be willing to talk to us further about PPI members on data monitoring committees. (leave blank if you do not want to be contacted further)

23. Please provide your email address if you would like to be notified when results of this survey have been analysed and published and to be entered for the prize draw for a £50 gift voucher. (leave blank if you do not want to be notified or entered for the prize draw)

Thank you for completing the survey.

The information you have given will be used to form a plain English summary, which we hope can be used to improve practices of clinical trials in your country and others around the world.

If you have additional questions about this survey, please email nurulamin.noor.18@ucl.ac.uk

Appendix 10: Topic guide for interviews with trialists and PPIE representatives on DMCs

1. Interviewer name	Nurulamin Noor
2. Participant ID#	
3. Interview date (mm/dd/yyyy)	|___|___|/|___|___|/|___|___|___|___|
4. Participant agrees to audiovisual recording	☐ Yes ☐ No
5. Time interview began (hh:mm)	|___|___ | : |___|___| pm
6. Time interview ended (hh:mm)	|___|___| : |___|___| pm

Step 1: Complete Q1—3 above before starting the interview.

Step 2: Introduce yourself at the beginning of the interview.

Step 3: Thank participant for taking part in the interview.

Step 4: Read *Section 1: Information about the study* to the participant.

Step 5: Ask for the participant's permission to record the interview.

Step 6: Press audio recording button if permitted. Document time.

Step 7: Conduct interview.

Step 8: Thank the participant at the end of the interview. Ask if questions.

Step 9: Document time interview ended above.

Step 10: Ask participants if they want a summary of the interview findings and if I can contact them in future with results of project.

Section 1: Introduction (approximately 10 minutes)

- Welcome, introduction of interviewer.
- Explain about qualitative interview process and aims of this qualitative research to find out about experiences and opinions of PPI and DMCs – and secondary aim to also explore more innovative clinical trial designs.
    - First part of project – review of DMC composition practices to date, then performed 2 large global surveys for individuals working in field of clinical trials and individuals self-identifying as PPI representatives or involved in PPI.
    - This is second part undertaking interviews to explore in detail about experiences and opinions.
    - Third part of project will be aiming to develop consensus guidance with a large multi-disciplinary team of individuals from the UK and around the world.
- Confirm that this project being undertaken as part of a PhD at the Medical Research Council Clinical Trials Unit with a broad multi-disciplinary team across the UK including PPI representatives.
- Confirm that they have been picked as interview participant as indicated they have been an independent member of a DMC before. Therefore keen to understand experiences on how things worked and if any improvements could occur in process.
- Any questions, then confirm consent, then proceed with interview if happy to do so.
- Confirm consent (from previously emailed consent form) to take part in this qualitative interview and confirm consent for audio recording of interview.
    - Read the information sheet and had questions answered.
    - Understand that voluntary to take part and can withdraw or ask for the interview to be stopped at any stage and that if they do not wish for their answers to be used for subsequent work, then that it will not be used.
    - Explain about requirement for audio recording and process of anonymised transcription, where the anonymised transcripts are then analysed for common themes and findings.
    - Explain about reimbursement and process/timeline for this.
    - All data anonymised, so any comments/quotes if used in publications would be done without identifying any individuals or organisations that they may work within.
    - Explain about approximate timings for the interview but explain that if the interviewee would like to finish slightly earlier or indeed have slightly more to discuss then that would be fine to do so.
    - Happy to proceed and take part?
    - Ask if individual would like to receive summary of their transcribed data? (add-on question)

- Start record (ask interviewee to confirm acceptance of recording)

Section 2: Discussion (approximately 30-40 minutes)

Background of the interviewee

- Ask to confirm their main role(s) in clinical trials

Motivation for taking part in this interview

- Thank interviewee for taking part and ask them to explain their motivations for taking part today?
- What hoping to get out of taking part individually?

Experience and opinions of DMCs in general

- Establish personal experience on DMCs and in what roles
- Typical composition of DMCs
- Opinion on best make-up for DMCs
- How selected? What criteria for selection?
- How should be selected? Who should be responsible for selecting?
  - Subjective opinion on what constitutes experienced enough
- Funding bodies involved in selection? Should they be involved?
- How often to meet? What is the best format for meetings?
- Any instances of conflict?
- Should protocol, SAP, all manuscripts, some manuscripts be reviewed by DMC prior to submission?
- DMC role in future data sharing of trial?

Experiences of DMCs during novel and complex trials

- How they would define novel and complex trials?
- Should timing for meet, interim analyses, last look at data etc. be different for these trials?
- Any experience in real life of DMCs within these trials? Any difference to DMC conduct during these trials?
- Are more experienced individuals needed for these DMCs?

Acknowledgement for DMCs

- How done currently? Academia vs industry?
- How would be best done?
- Any examples where independence could be compromised?
  - Payment, publications etc.

Independence of DMCs

- Experiences of DMC independence and if ever compromised?
- Specifically if funding bodies ever on DMCs

Inform of both surveys indicated either that a PPI representative should either be on the DMC or be considered. Therefore in context of those findings, eager to explore further.

Opinions of PPI on DMCs

- Open question on whether this should always be the case or not?
- In which instances - all the time, some of the time, never? Why this answer?
- Pros – perceived?
- Cons – perceived?
- Challenges – perceived?

Experience of PPI and DMCs

- Ask about experience of PPI specifically on DMCs?
- Elaborate on specific details, logistics and experiences of this process?
- Pros – actual/experienced?
- Cons – actual/experienced?
- Challenges – actual/experienced?
- Do novel/complex trials change opinions on PPI on DMCs for these types of trials?
- Do types of medical condition change opinions on PPI on DMCs?

Opportunity for PPI on DMCs

- Who would be best placed for PPI role on DMCs?
    - What previous roles would help? Why, what skills do these roles develop?
- How can this best be provided?
- Who/which organisation(s) would be in best position to help?
- What would constitute experienced enough for PPI on DMCs?
- What is perception of why PPI not routinely on DMCs? How could this be challenged/overcome?
- What are thoughts on more than one PPI representative? How would that affect group dynamic in already small trial oversight committees?
- How best to recognise contributions of PPI members? Should this be different to non-PPI members?
- Do you think most others would accept PPI role on DMCs if offered?

Training for PPI and/or all staff to be on DMCs

- What is role for training on DMCs?
- Establish if ever received any training to date or planned?
- How can this best be provided?
- What would be benefits?
- Who/which organisation(s) would be in best position to help?

Other

- If anything important that would like to discuss on topic that has not been mentioned or asked about?

Section 3: Conclusion (approximately 10 minutes)

- Sum up what has been discussed and ask if anything to add?
- How did interviewee find the process?
- Thank interviewee for their time
- Ask interviewee if they would like transcribed copy of their interview
- Confirm that interview will be transcribed and anonymised, then audio recording deleted
- Confirm that transcription will be kept in secure manner using UCL data safe haven
- Anonymised data will be compiled together across interviews and then analysed for common themes and findings.
- Aim to share the results, and that will be open access.
- Provide contact details if wish to follow-up on any issues talked about today and to provide contact email address: nurulamin.noor.18@ucl.ac.uk