# Inhibition of WEE1 Is Effective in TP53and RAS-Mutant Metastatic Colorectal Cancer: A Randomized Trial (FOCUS4-C) Comparing Adavosertib (AZD1775) With Active Monitoring

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PURPOSE Outcomes in RAS-mutant metastatic colorectal cancer (mCRC) remain poor and patients have limited therapeutic options. Adavosertib is the first small-molecule inhibitor of WEE1 kinase. We hypothesized that aberrations in DNA replication seen in mCRC with both RAS and TP53 mutations would sensitize tumors to WEE1 inhibition.

METHODS Patients with newly diagnosed mCRC were registered into FOCUS4 and tested for TP53 and RAS mutations. Those with both mutations who were stable or responding after 16 weeks of chemotherapy were randomly assigned 2:1 between adavosertib and active monitoring (AM). Adavosertib (250 mg or 300 mg) was taken orally once on days 1-5 and days 8-12 of a 3-week cycle. The primary outcome was progression-free survival (PFS), with a target hazard ratio (HR) of 0.5 and 80% power with a one-sided 0.025 significance level.

RESULTS FOCUS4-C was conducted between April 2017 and Mar 2020 during which time 718 patients were registered; 247 (34%) were RAS/TP53-mutant. Sixty-nine patients were randomly assigned from 25 UK hospitals (adavosertib = 44; AM = 25). Adavosertib was associated with a PFS improvement over AM (median  $3.61 \text{ v} \cdot 1.87 \text{ months}$ ; HR = 0.35; 95% CI, 0.18 to 0.68; P = .0022). Overall survival (OS) was not improved with adavosertib versus AM (median 14.0 v 12.8 months; HR = 0.92; 95% CI, 0.44 to 1.94; P = .93). In prespecified subgroup analysis, adavosertib activity was greater in left-sided tumors (HR = 0.24; 95% CI, 0.11 to 0.51), versus right-sided (HR = 1.02; 95% CI, 0.41 to 2.56; interaction P = .043). Adavosertib was well-tolerated; grade 3 toxicities were diarrhea (9%), nausea (5%), and neutropenia (7%).

**CONCLUSION** In this phase II randomized trial, adavosertib improved PFS compared with AM and demonstrates potential as a well-tolerated therapy for RAS/TP53-mutant mCRC. Further testing is required in this sizable population of unmet need.

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# **ASSOCIATED** CONTENT Appendix

# **Data Supplement** Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Targeting the cellular DNA damage response (DDR) has been an effective therapeutic strategy in several tumor sites, including ovarian and pancreatic cancer.<sup>1,2</sup> These agents can be used as monotherapy in cancers with defective DDR, where we might anticipate a synthetic lethality interaction: two pathways together perform an essential function, and the loss of one pathway (eg, because of mutation) is tolerated but the loss of both pathways leads to cell death.<sup>3</sup>

WEE1 is a nuclear tyrosine kinase that has a central role in cell cycle regulation, including being the key regulator of the G2/M checkpoint through actions on CDK1,4 optimizing DNA-histone stoichiometry before mitotic

entry<sup>4</sup> and modulation of CDK1/2 during the intra-S phase to block replication initiation.<sup>5</sup> Inhibition of WEE1 causes unscheduled entry into mitosis, aberrant firing of replication origins leading to dNTP (Dithiobis [5-nitropyridine]) shortage and replication stress,4 and accumulation of DNA damage during S phase, leading to increased reliance on the G1/S checkpoint.4 Adavosertib (AZD1775) is the first small-molecule inhibitor of WEE1 kinase and has been tested in combination with chemotherapy and radiotherapy<sup>6,7</sup> but more recently as monotherapy to generate synthetic lethality in tumors with DDR defects.6

There has been limited investigation into agents targeting the DDR in metastatic colorectal cancer

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#### CONTEXT

## **Key Objective**

To test if adavosertib, which is a small-molecule inhibitor of the WEE1 kinase, is effective as monotherapy in patients with *RAS/TP53*-mutant metastatic colorectal cancer (mCRC) as maintenance therapy following induction chemotherapy.

## **Knowledge Generated**

In this phase II randomized trial, adavosertib was well-tolerated and improved progression-free survival in *RAS/TP53*-mutant mCRC compared with active monitoring. Treatment effect may be affected by primary tumor location and *KRAS* subtype, with greater benefit seen in left-sided cancers and those with *KRAS* codon 12/13 mutations. *RAS/TP53* subgroup is a distinct moderately poor prognostic population.

#### Relevance

Adavosertib is a promising therapeutic agent in patients with *RAS/P53*-mutant mCRC, a poor prognostic population of unmet need, and was well-tolerated. This study demonstrates the potential of targeting the DNA damage response pathway in mCRC, which should be a research priority. Future studies of adavosertib should stratify patient outcomes according to primary tumor location and *RAS* subtype.

(mCRC), mainly because of the lack of systematic identification of alterations in DDR genes.8 Here, we test adavosertib in RAS- and TP53-mutant (RAS/TP53-mut) mCRC, which we hypothesize would be sensitive to WEE1 inhibition. TP53 is a key regulator of the G1/S checkpoint<sup>9</sup>; loss of function leads to dependence on the intra-S and G2/M checkpoints to detect DNA damage and initiate repair. 10 In preclinical studies, AZD1775 possessed preferential killing effect in TP53-deficient compared with TP53 wild-type tumors. 11 Mutant RAS, as well as recognized actions through downstream mitogenactivated protein kinase B (MAPK-AKT) pathway signaling, also drives cell cycle progression leading to replication stress during S phase. 12 In preclinical studies, mutant RAS drives cells into S phase through regulation of the CDK4 or CDK6 complex and provides sustained mitogenic signals through sustained CDK2 activity. These effects activate the replication stress response including checkpoint activation. 13 Theoretically, RAS/TP53-mut tumors will be highly vulnerable to adavosertib, with G1 checkpoint failure, evidence of replication stress, and reliance on the intra-S phase and G2/M checkpoints.

The FOCUS4 trial program was an adaptive molecularly stratified umbrella platform trial that evaluated the safety and efficacy of novel treatments in targeted biomarker subgroups within a phase II/III trial setting in the interval after 16 weeks of first-line therapy of mCRC. The design has been published separately, <sup>14</sup> and the trial schema, registration, and biomarker methods are provided in the Data Supplement (online only). Here, we report the findings of FOCUS4-C, which tested the safety and efficacy of adavosertib in patients with *RAS/TP53*-mut mCRC compared with active monitoring (AM) and has achieved disease stability following induction chemotherapy.

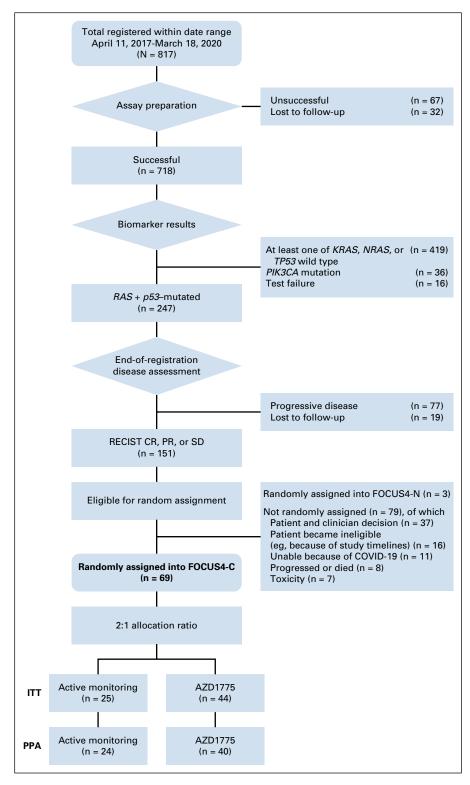
## **METHODS**

# Trial Approvals, Patient Eligibility, and Recruitment

The trial and subsequent amendments were approved by the UK National Ethics Committee Oxford—Panel C (reference 13/SC/0111) and by the relevant regulatory body MHRA (CTA No. 20363/0400/001 and EudraCT No. 2012-005111-12).

Patients age more than 18 years with newly diagnosed mCRC were registered into the FOCUS4 trial program, while undergoing induction chemotherapy, from a total of 88 UK hospitals. Following registration, a tumor sample was tested using next generation sequencing platform for stratification into molecular subtypes including *BRAF*, *PIK3CA*, *TP53*, and *RAS* mutations (Fig 1 and Data Supplement). Patients were required to provide written informed consent for both tissue testing and entry into any of the randomized subtrials including FOCUS4-C.

Patients were randomly assigned into the FOCUS4-C trial in a subset of 25 hospitals between July 2017 and March 2020. Patients were eligible if their tumor had both *RAS* and *TP53* mutations and they had disease stability or response as assessed by computed tomography (CT) scan at the end of 16 weeks of induction chemotherapy, at which point the chemotherapy ceased and the patient was randomly assigned. Patients required a baseline CT scan 4 weeks before random assignment, a minimum 3-week washout period between the last dose of chemotherapy or biologic therapy and the first dose of adavosertib, adequate renal (creatinine clearance > 50 mL/min) and liver function, a WHO performance status of 0-1, and no evidence of prolonged QT interval on ECG.



**FIG 1.** Flowchart of patients through the trial. CR, complete response; ITT, intention-to-treat; PPA, perprotocol analysis; PR, partial response; SD, stable disease.

## **Trial Procedures**

Adavosertib was supplied by AstraZeneca Ltd (Cambridge, UK); packaging, labeling, and distribution were undertaken by Fisher Services (Horsham, UK). Patients randomly

assigned to adavosertib continued the drug until disease progression, death, or intolerable toxicity. The first 21 patients received adavosertib 250 mg once daily, on days 1-5 and 8-12 of a 3-week cycle. The next 23 patients received

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adavosertib 300 mg once daily, on the same schedule. Patients took an oral 5HT3 antagonist with each dose, and oral dexamethasone 4 mg was given on day 1 and day 8 of each cycle unless clinically contraindicated.

Because of the mandatory supportive medication for nausea and vomiting for which a placebo was not available, blinding was not possible, and AM was used as the control arm. Patients randomly assigned to AM followed the same follow-up schedule and remained off any other anticancer treatment until clinical or radiologic evidence of disease progression.

Patient tumor status was assessed at the treating hospital every 8 weeks by CT scan, according to RECIST, version  $1.1.^{15}$  Toxicities and symptoms were assessed locally every 4 weeks, using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Patients remained on trial until disease progression occurred, at which point the patient was recommended to restart the same chemotherapy that was used in the induction phase. Treatment was stopped in the event of grade 3 or worse toxic effects or persistent toxicities judged medically significant or not tolerated by the patient, until the toxicity resolved to grade 1 or better.

#### Statistical Methods

A full description of the statistical methods is provided in the Data Supplement. In summary, patients were allocated to either adavosertib or AM, using a 2:1 allocation ratio by minimization with a 20% random element. All analyses were performed according to a predefined statistical analysis plan using Stata (version 16.1; Stata Corporation, TX). The primary outcome measure was progression-free survival (PFS), and the prespecified primary efficacy analysis was a per-protocol analysis (PPA) using Cox regression adjusting for minimization factors. Intention-to-treat (ITT) and unadjusted models were also performed as secondary analyses. Sample size calculations were based upon a target hazard ratio (HR) of 0.5 with 80% power and .025 one-sided alpha requiring a target of 26 PFS events in the control arm for final analysis.

## **RESULTS**

## **Recruitment and Patient Characteristics**

The FOCUS4 trial program ran between January 2014 and March 2020. FOCUS4-C ran between April 2017 and March 2020, during which time 817 patients were registered, of whom 718 underwent successful biomarker profiling (Fig 1 and Data Supplement). Two hundred forty-seven patients (34%) had tumors confirmed with both *RAS* and *TP53* mutations (*RAS/TP53*-mut). Of these, 151 had stable or responding disease after 16 weeks of first-line treatment and 69 were randomly assigned using a 2:1 ratio: 44 to adavosertib and 25 to AM. Of the remaining eligible 82, two chose to be randomly assigned into the concurrent FOCUS4-N trial and others chose not to be randomly

assigned into FOCUS4 for reasons such as toxicity from first-line therapy or patient-clinician choice to seek alternative pathways.

Table 1 summarizes the patient baseline characteristics. There were some minor imbalances, which are corrected for in the adjusted analysis (primary model). There were no differences in the frequency of other molecular alterations between the groups. There were no significant differences between the registration period chemotherapy regimens in the adayosertib and AM arms.

# Primary Analysis: PFS (per-protocol)

Five patients were excluded from the PPA: four did not start treatment (adavosertib arm) and one was subsequently found to have had progressive disease at the point of random assignment (AM arm). One patient was censored early when they received fluorouracil as anticancer treatment before progression (AM arm).

Within the primary PPA (n = 64), there were 40 of 40 PFS events in the adavosertib arm and 22 of 24 in the AM arm. Patients treated with adavosertib had a longer PFS than those on AM (3.61  $\nu$  1.87 months). Both unadjusted HR (0.52; 95% CI, 0.30 to 0.89; P = .022) and adjusted HR (0.35; 95% CI, 0.18 to 0.68; P = .0022) were statistically significant. Kaplan-Meier curves are provided in Figure 2.

## PFS (ITT)

All patients were included in the ITT analysis, but four patients were censored the day after random assignment: three in the adavosertib arm (two because of patient withdrawal and one without any post–random assignment CT scan assessments) and one in the AM arm without any post–random assignment CT scan assessments.

There were 41 of 44 PFS events in the adavosertib arm and 23 of 25 in the AM arm. Consistent with the PPA, the ITT PFS analysis shows a PFS advantage with adavosertib over AM in both the unadjusted (HR = 0.55; 95% CI, 0.32 to 0.94; P=.032) and adjusted analyses (HR = 0.40; 95% CI, 0.21 to 0.75; P=.0051).

# Overall Survival (ITT)

There were 27 of 44 deaths in the adavosertib arm and 16 of 25 in the AM arm. There was no significant overall survival (OS) benefit with adavosertib compared with AM (median survival 14.0 v 12.8 months; unadjusted HR = 0.79; 95% CI, 0.42 to 1.48, P = .47; adjusted HR = 0.92; 95% CI, 0.44 to 1.94, P = .93; Fig 2).

# **Tumor Control**

Adavosertib was associated with a higher proportion of patients with disease control compared with AM (47%  $\nu$  28% at any time during the trial), including one patient with a documented partial response to adavosertib (Data Supplement).

TABLE 1. Baseline Patient Characteristics by Randomized Group

Characteristic	Active Monitoring (n = 25)	Adavosertib (n = 44)
Mean (SD) age, years	61.9 (12.2)	59.2 (12.8)
	No. (%)	No. (%)
Sex		
Male	15 (60)	31 (70)
Female	10 (40)	13 (30)
Current WHO performance status		
0	17 (68)	35 (80)
1	8 (32)	9 (20)
Site of primary tumor		
Right colon	9 (36)	13 (30)
Left colon	6 (24)	13 (30)
Rectum	10 (40)	18 (41)
Current state of primary tumor		
Resected primary	9 (36)	23 (52)
Unresected primary	16 (64)	19 (43)
Unresected local recurrence	0 (0)	2 (5)
Timing of metastases		
Metachronous	4 (16)	13 (30)
Synchronous	21 (84)	31 (70)
No. of metastatic sites		
One	6 (24)	16 (36)
Two or more	19 (76)	28 (64)
Disease assessment at end of first-line treatment		
Complete response	0 (0)	1 (2)
Partial response	13 (52)	26 (59)
Stable disease	12 (48)	17 (39)
First-line treatment regimen		
FOLFOX	7 (28)	15 (34)
FOLFIRI	8 (32)	14 (32)
CAPOX	6 (24)	11 (25)
FOLFOXIRI	3 (12)	3 (7)
Others	1 (4)	1 (2)
PIK3CA mutation status		
Mutation	1 (4)	1 (2)
Wildtype	24 (96)	43 (98)
Total	25 (100)	44 (100)

Abbreviations: CAPOX, capecitabine and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil, oxaliplatin, and irinotecan; SD, standard deviation.

## Subgroup Analyses

The impact of adavosertib versus AM on PFS was explored in prespecified subgroups (Fig 3). The most marked difference in effect was for primary tumor location (PTL):

patients with a right PTL had no PFS advantage with adavosertib compared with AM (1.87 v 1.91 months; HR = 1.02; 95% CI, 0.41 to 2.56), whereas those with a left PTL did (3.61 v 1.87 months, HR = 0.24; 95% CI, 0.11 to 0.51; interaction P = .043; Data Supplement).

This prompted an unplanned subgroup analysis of PTL on OS, and although the numbers of events were low, the interaction was even more marked (Data Supplement). Median OS was 14.1 versus 11.3 months for adavosertib versus AM in left PTL (adjusted HR = 0.37; 95% CI, 0.15 to 0.87) but was 6.5 versus 15.5 months in right PTL (HR = 6.5; 95% CI, 0.72 to 6.43; interaction P = .0032). In terms of response, 38% of right-sided adavosertib patients versus 42% of right-sided AM patients reported disease stability or response at least once while on trial, whereas for left-sided tumors, the figures were 53% versus 19%.

Patients who had responded to induction chemotherapy (v stable disease) and who had two or more metastatic sites appeared to benefit more from adavosertib, albeit to a lesser degree (interaction P value = .14 for response to induction; P = .12 for number of metastatic sites; Fig 3).

# External Analyses to Further Characterize the RAS/TP53-Mut Biomarker Population

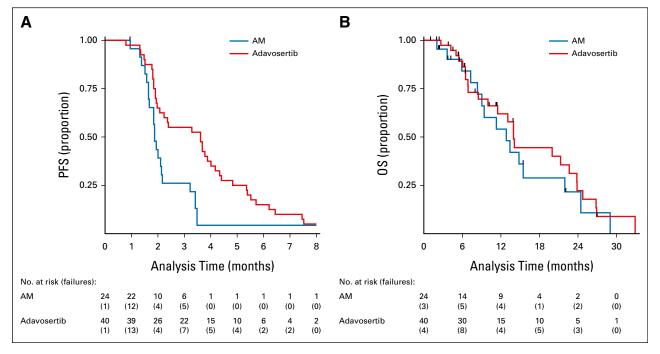
The *RAS/TP53*-mutant population has not been previously described. To understand the prognostic implication of this alteration, we analyzed the outcomes of a subset (n = 438) of patients from the FOCUS trial in whom the S:CORT consortium had analyzed a wider panel of CRC genes including *KRAS*, *NRAS*, *BRAF*, *MSI*, and *TP53*. The *RAS/RAF* wild-type group was the reference population (median OS 21.6 months). The *RAS/TP53*-mutant population is distinct from either mutation alone (*RAS* or *TP53*) and had a worse prognosis than either in isolation with a median OS of 14.9 months (HR = 2.06; 95% CI, 1.08 to 3.93; P = .028; Fig 4). This suggests that the *RAS/TP53*-mut population is a poor-prognosis subgroup but not as marked as for patients with a *BRAF* mutation or microsatellite instabilityhigh tumor.

These data are consistent with the finding that during the registration period of FOCUS4, 33% of patients in the *RAS/TP53*-mut population experienced progression during the first 16 weeks of chemotherapy. This is similar to the rate in the *BRAF*-mutant group (34% progressed) but higher than that seen in *RAS*-mutant (24%) and all wild-type (22%) subgroups (Data Supplement).

# Effect of *RAS* and *TP53* Mutation Subtypes on Adavosertib Activity

We observed that patients with KRAS codon 12/13 mutations had a significant benefit from adavosertib (P for interaction = .014; Fig 3), whereas no detectable benefit was observed in those with KRAS mutations at other codons or with NRAS mutation. Furthermore, the interaction effects of KRAS subtype and of PTL on PFS may be additive as

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**FIG 2.** (A) PFS (primary analysis) in PPA population: Cox regression, adjusted for minimization factors—HR = 0.35 (95% CI, 0.18 to 0.68), P = .0022. Minimization factors: location of primary tumor (left, right, and rectum), baseline WHO performance status, baseline disease assessment, number of metastases, and first-line therapy (fluoropyrimidine, oxaliplatin or irinotecan, and monoclonal antibody). (B) OS (secondary analysis) in PPA population: Cox regression, adjusted for minimization factors—HR = 0.86 (95% CI, 0.39 to 1.86), P = .70. Minimization factors: location of primary tumor (left, right, and rectum), baseline WHO performance status, baseline disease assessment, number of metastases, and first-line therapy (fluoropyrimidine, oxaliplatin or irinotecan, and monoclonal antibody). AM, active monitoring; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPA, per-protocol analysis.

there is a significant benefit from adavosertib within the subgroup of left PTL KRAS codon 12/13 subtypes (HR = 0.16; 95% CI, 0.05 to 0.50) and a clear disbenefit within the subgroup of right PTL noncodon 12/13 subtypes (HR = 1.56; 95% CI, 0.49 to 4.97; Data Supplement). The subtype of TP53 mutation or the co-occurrence of PIK3CA mutation did not affect outcome.

## **Toxicity and Compliance**

There was good compliance with randomized allocation, and adavosertib was generally well-tolerated (Fig 5 and Data Supplement). Compared with AM, adavosertib was associated with increased reported toxicity (≥ grade 1), most notably increased frequency of diarrhea (61% v 28%), fatigue (75% v 56%), nausea (68% v 32%), and vomiting (41% v 4%). However, the majority of such toxicity was of low grade, with 9% in the adavosertib arm reporting diarrhea of  $\geq$  grade 3, 11% fatigue, 5% nausea, and 2% vomiting, versus none of each in the AM arm. As described, during the trial, there was an increase in the dose of adavosertib from 250 mg to 300 mg. The higher dose was associated with an increased frequency of grade 3 diarrhea (14% v 4%), but otherwise the toxicity profile was similar, and with similar rates of dose modifications and delays.

#### Impact of Adavosertib Dosing

As described, during the trial, there was an increase in the dose of adavosertib from 250 mg to 300 mg. PFS was 2.2 months (HR = 0.58; 95% CI, 0.31 to 1.06) with the 250-mg dose and 3.7 months (HR = 0.47; 95% CI, 0.25 to 0.89) with the 300-mg dose; this difference was nonsignificant (P=.48; Data Supplement). Between the 250-mg and 300-mg doses, there was an increased frequency of grade 3 diarrhea (4% v 14%), but otherwise the toxicity profile was similar. There were similar rates of dose modifications between the 250-mg and 300-mg doses: dose delays (16% v 7%), dose reductions (4% v 5%), and dose omissions (19% v 17%). A swimmer plot integrating the effects of adavosertib dose, randomized group, and PTL on PFS is shown in the Data Supplement.

#### **DISCUSSION**

Here, we have reported that FOCUS4-C met its primary end point; patients with *RAS/TP53*-mutant mCRC had PFS advantage with adavosertib compared with AM following induction chemotherapy. These results are particularly encouraging as *RAS/TP53*-mutant mCRC is a poor prognostic population with limited treatment options. Adavosertib was well-tolerated at both doses evaluated.

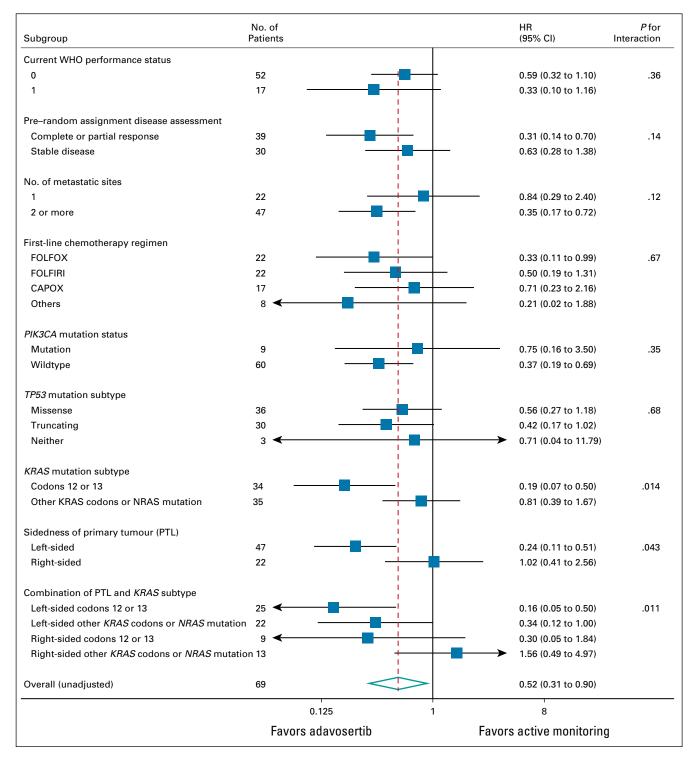


FIG 3. Subgroup analyses for PFS by intention to treat. CAPOX, capecitabine and oxaliplatin; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; PFS, progression-free survival; PTL, primary tumor location.

test novel agents efficiently with specified biomarker subgroups in mCRC with the multi-arm, multi-stage design allowing for an early signal of drug inactivity<sup>14</sup>; thus, any demonstrated efficacy would require further confirmatory

The overarching aim of the FOCUS4 trial program was to study to lead to practice change. FOCUS4-C represents a success of this approach, efficiently demonstrating promising activity of adavosertib within patients with RAS/ P53-mutant mCRC, and will directly influence research practice in mCRC.

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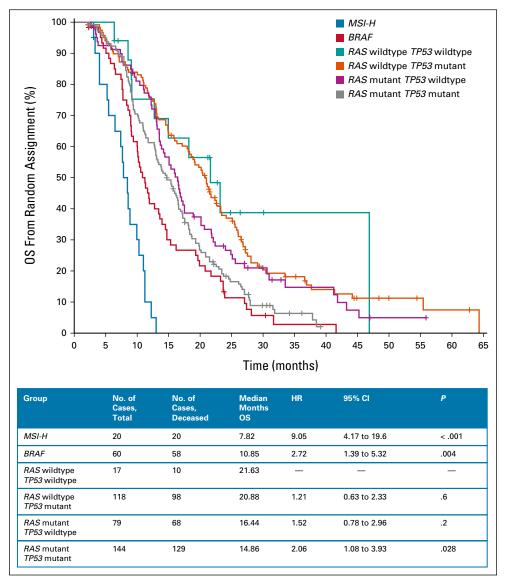


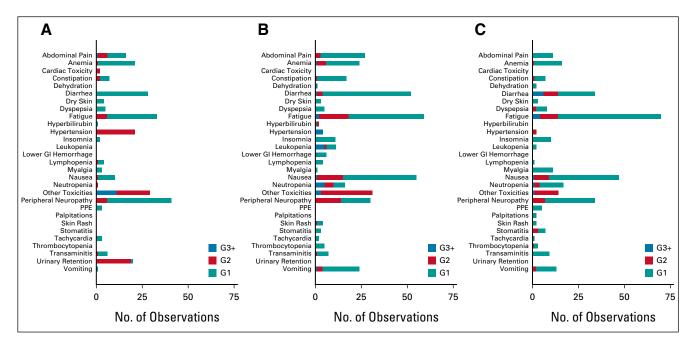
FIG 4. Prognostic impact of biomarker subgroups on OS in previous FOCUS trial. HR, hazard ratio; MSI-H, microsatellite instability-high; OS, overall survival.

The intermittent treatment strategy used in FOCUS4 follows the demonstration of no detriment in OS in the MRC COIN trial. This is now further substantiated by an individual participant data meta-analysis. <sup>16</sup> Thus, AM is an accepted standard of care following a few months of first-line therapy. FOCUS4 was specifically designed to use this window following first-line induction chemotherapy to test novel agents in specified biomarker groups, before the evolution of multiple resistance mechanisms. <sup>14</sup>

A prespecified analysis demonstrated that adavosertib activity was limited to left colon and rectal PTL, with little activity observed in right PTL. Having observed the significant subgroup effects on PFS, we investigated possible impact on OS. It is provocative to see that in the left-sided tumors, OS was significantly improved with median OS from random assignment increasing from 11.3 months to 14.1

months (HR = 0.40; 95% CI, 0.17 to 0.97). There is also a possibility of adverse effect on outcome in patients with right PTL. However, the number of patients and events was limited and thus, any conclusions need to be cautious in relation to this observed effect on OS in both subgroups. Differences in CRC by PTL are well-documented, in terms of biology, prognosis, and treatment response,  $^{17}$  but the mechanisms for differences of treatment efficacy by PTL are not well-understood.

An exploratory analysis showed that adavosertib had the most PFS effect in patients with *KRAS* codons 12/13/*TP53*-mutant tumors, with lesser activity in those with extended *KRAS*, or *NRAS* mutations; functional differences between *RAS* isoforms are documented. <sup>18</sup> Despite the small sample sizes in FOCUS4-C, the PTL and *RAS* subtypes subgroup analyses showed interactions significant at the 5% level.



**FIG 5.** Cumulative reported toxicity, within FOCUS4-C treatment groups and with initial AZD1775 doses separated: (A) active monitoring (n = 25), (B) AZD1775 250 mg (n = 23), and (C) AZD1775 300 mg (n = 21). G, grade; PPE, palmar plantar erythema.

Although these subgroup analyses provide provocative results, we lack a mechanistic explanation for these differences in adavosertib effect; ongoing translational work shall investigate this. We would recommend that further clinical development of adavosertib in the *RAS/TP53*-mut mCRC population should not be limited by PTL or *RAS* subtype but should include close monitoring of patients with right PTL and extended *RAS* mutations to ensure that neither futility nor detriment are observed.

Although the clinical implications of the *RAS/TP53* mutation in mCRC are not well-studied, each alteration is individually well-characterized. Here, we have shown that the double *RAS/TP53*-mutant subgroup carries a moderately poor prognosis (Fig 4) and appears to confer a worse prognosis than either mutation in isolation. This biomarker subgroup has thus shown distinct prognostic and therapeutic relevance and so merits further study in translational work, existing data sets, and ongoing therapeutic trials in mCRC.

Adavosertib has demonstrated an acceptable safety profile; the main toxicity was diarrhea. Efficacy was noted at both the 250-mg and 300-mg doses, with a suggestion of additional activity with the higher dose. We would therefore recommend the 300-mg dosing to progress to further clinical studies in fit patients. However, in the treatment-refractory setting, the 250-mg dose may be more tolerable.

There are limitations to this study. We considered, and would have preferred, a placebo-controlled design; however, at the time of launching FOCUS4-C, high rates of

nausea and vomiting had been observed in other adavosertib trials and high-dose steroid antiemetics were considered necessary. For this reason, both clinicians and patient representatives considered a placebo design unfeasible. Given the favorable safety data for single-agent adavosertib in FOCUS4-C, placebo-controlled design could be considered in the future. It is possible therefore that the PFS effect observed was influenced by investigator and patient preference to restart first-line chemotherapy sooner in the AM arm. However, a marked difference in effect was observed between the right and left PTL groups treated with adavosertib, suggesting a lesser effect on the primary analysis because of this potential bias. Additionally, the PFS end point was not centrally reviewed, but assessed in individual sites by RECIST criteria. A further limitation is that by testing adavosertib in the maintenance setting and requiring stability following induction chemotherapy, we have excluded the RAS/TP53 patients with the worse outcome. We therefore cannot generalize the effect of adayosertib within this entire biomarker group.

In conclusion, adavosertib (AZD1775) has demonstrated promising activity compared with AM in patients with *RAS/TP53*-mut mCRC. This treatment benefit may relate to PTL and *KRAS* subtype. Given this clear demonstration of efficacy in an RCT and acceptable toxicity profile, future clinical development of adavosertib is warranted particularly as it may represent a future treatment opportunity in this sizable population of unmet need.

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## **EQUAL CONTRIBUTION**

J.F.S., L.C.B., and D.F. contributed equally to this work as first authors. M.S. and T.S.M. contributed equally to this work as last authors.

#### **SUPPORT**

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## **CLINICAL TRIAL INFORMATION**

ISRCTN#90061546

# AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.01435.

## **DATA SHARING STATEMENT**

Individual deidentified participant data (including data dictionaries) can be shared upon appropriate application to the MRC CTU at any time from full publication. Study protocols and statistical analysis plan have been provided in the Data Supplement with this manuscript. Going forward, it is proposed that data will be shared with an appropriate international collaborative repository to enable future IPD meta-analysis.

## **AUTHOR CONTRIBUTIONS**

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

## **ACKNOWLEDGMENT**

The full list of FOCUS4 Trial Investigators can be found in Appendix 1.

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Inhibition of WEE1 Is Effective in TP53- and RAS-Mutant Metastatic Colorectal Cancer: A Randomized Trial (FOCUS4-C) Comparing Adavosertib (AZD1775) With Active Monitoring

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/ico/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.

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Cameron D. (Chair), Souhami R., Peeters M., Billingham C., Griffiths G., and Brown J.

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Johnson P. (Chair), Rudd R., Whelan J., and Russell A.

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076)

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Western General Hospital	Ewan	Brown (PI)
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	Caroline	Bruce
	Patricia	Campbell
	Sally	Clive
	Kathryn	Connolly
	Lorraine	Cook
	Helen	Creedon
	Judith	Crawford
	Alisa	Davinson
	Lesley	Dawson
	Grace	Ding (Tze-en Ding)
	(continued in next col	umn)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Doak
Doig
Dunbar
Elliott
Faragher
Fineron
Gilluley
Kondarewicz
Lauchlan
Macpherson
Mclean
Milligan
Muir
Oswald
Pheely
Phillips
Rust
Siddiqui
Stanley
Stewart
Wilson
Collinson (PI)
Seymour (PI)
Abbas
Ajibayo
Anthoney
Ali
Appell
Barker
Barlow
Begum
Berry
Chapman
Charlton
Clark
e Crawford
Crossley
Dart
Docherty
Ershova
Firth

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principal investigator [PI])
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	Leanne	Galloway-Browne		Maria	Evans
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	Amelie	Harle		Jill	Halpin
	Farzana	Haque		Robert	Henley
	Janine	Heeley		Lynda	Holman
	Jane	Hook		Alys	Irving
	Jane	Hughes		Amanda	Jackson
	Alison	Judge		Emma	John
	Emma	Livesey		Rhianydd	Jones
	Emma	Lundy		Colette	Kemp
	Michael	O'Brian		Satish	Kumar
	Mike	Osborne		Claire	Lang
	Lauren	Paul		Cindy	Langford
	Mary	Perrin		Debbie	O'Connor
	Annet	Pillai		Diana	Osman
	Charlotte	Richardson		Catherine	Matthews
	Suzanne	Rogerson		Ross	McLeish
	Olorunda	Rotimi		James	Morgan
	Emily	Rudolph		Phillip	Morgan
	Jenny	Seligmann		Renata	Poole
	Hannah	Shanks		Karen	Pow
	Daniel	Swinson		Joanne	Preece
	Danny	Ulahannan		Cathy	Richards
	Mariah	Vorajee		Jayne	Richards
	Sarah	Wetherop		Rosie	Roberts
	Hannah	Wigginton		Sharon	Rogers
	Christopher	Williams		Jodie	Sherburn
	Jawairiya	Zubair		Lisa	Stafford
Velindre Hospital	Rob	Jones (PI)		Catherine	Sullivan
	Richard	Adams (PI)		Hana	Thomas
	Seema	Arif		Anshu	Wadhawan
	Rebecca	Bethell		Catherine	Watkins
	Kathy	Bishop		Hilary	Williams
	Alison	Brewster		Rachel	Williams
	Michael	Brown		Kay	Wilson
	Julie	Broughton		Rebecca	Wilson
	Lucy	Chestney		Cheryl	Worsey
	Nikki	Coates		Charlotte	Young
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	Karen	Davies		Jo	Allen
	Clare	Donnithorne		Hannah	Arhinful
	(continued in next co	lumn)		(continued on following	g page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Janet	Beech		Richard	Crossley
	Martin	Birch		Alice	Dewdney
	Anna	Bowron		Julia	Disney
	Suzanne	Carter		Lynne	Dixon
	Jackie	Connell		Paul	Dodd
	Camille	Cooney		Sarah	Gill
	Rebecca	Cox		Elizabeth	Hodgkinson
	Olive	Craven		Helen	Joyce
	Mark	Cutting		Mandip	Khaira
	Hannah	Downs		Panagiota	Kitsanta
	Karen	Forshaw		Jasima	Latif
	Chloe	Gawlik		Laura	Lee
	Jurjees	Hasan		Cathryn	Leng
	Sarah	Hughes		Tony	Matthew
	Paul	Husbands		Eileen	Marsh
	Mary	Jepson		Aimee	Pendlebury-Worrac
	Konstantinos-Vellios	Kamposioras		Megan	Perry
	Rhea	Langeveld		Simon	Pledge
	Catherine	McBain		Muneeb	Qureshi
	Danielle	McCool		Alison	Redfearn
	Saifee	Mullamitha		Helen	Shulver
	Monica	Narasimham		Helen	Slater
	Alkesh	Patel		Laura	Smith
	Jane	Rogan		Svetlana	Solovieva
	Mark	Saunders		Catherine	Spalton
	Sue	Seifi		Elisavet	Theodoulou
	Lilly	Simpson		Lucy	Walkington
	Greg	Wilson		Christopher	Walls
	Marie	Woolley		Mary	Ward
leston Park	Joanne	Hornbuckle (PI)		Katherine	Williams
Hospital				Vanessa	Wilshaw
	Jess	Aldred		Robin	Young
	Cyper	Allan	Bristol	Stephen	Falk (PI)
	Richard	Allen	Haematology		
	Lynne	Ashmore	and Oncology Centre		
	Darrell	Barrott		Elizabeth	Allison
	Alex	Bradshaw		Paul	Armenise
	Richard	Brown		Lindsay	Ball
	Sarah	Brown		Helen	Brooks
	Kevin	Chan		Paula	Byrne
	Rachael	Clarke		Carlota	Clemente
	Su	Clark		Marc	Coe
	Susan	Clenton	-	(continued on followin	

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
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	Kay	Drury		Christine	Cox
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	Elysia	Gower		Jane	Crozier
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	Robert	Hollister		Claire	Dyke
	Kirsten	Hopkins		Rachael	Exley
	Hollie	Jones		loana	Fodor
	Lauren	Joyce		Yuko	Francis
	Helen	Kingston		Sharath	Gangadhara
	Jayne	Leonard		Amy	Gaunt
	Amelia	Lowe		Jenny	Gilbert
	Catherine	McDonald		Beatrice	Hamilton
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	lan	Penwarden		Carey	Milsom
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Hospital				Abigail	Alford
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	Claire	Barron	-	Laura	Hart
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Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
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	Daniel	Lee		David	Barber
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	Paula	O'Reilly		William	Croxford
	Kristian	Plowman		Parth	Desai
	Karen	Shepherd		Kay	Ellel
	Karen	Stubbs		Cassandra	Gleeson
	Gabrielle	Taft		Louise	Hough
	Reenee	Tiam		Krishna	Panchal
	Adam	Wolstencroft		Shakeelah	Patel
/ictoria Hospital (Blackpool)	Sin	Lau (PI)		Mark	Pitt Preston
<u>·</u>	Charlotte	Armer		Sarah	
	Denise	Bennett	-	Andrew	Martyniak
	Caroline	Boardman		Aasif	Motala
	Oliver	Brennan		Deborah	Williamson
	Laura	Collins		Claire	Searle
	Falalu	Danwata		Shabbir	Susnerwala
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	Karen	Pollard		Alison	Chedham
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	Conor	Wilkinson		Emma	Gray
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Royal Preston	Sin	Lau (PI)		Lucy	Howell-Drewett
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Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
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	Dee	Lewis		Azeem	Saleem
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	Joanne	Rogers		Caroline	Ward
	Guillermo	Reina-Ruiz		Adrian	Zebrowski
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	Alison	Snell	Infirmary		
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Hammersmith	Harpreet	Wasan (PI)		Lisa	Horner
Hospital				Ibrar	Hussain
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	Craig	Macmillan		Stephanie	Lupton
	James	Maloy		Joanna	Lyle
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	Onyinye	Ndefo		Vishal	Ramdhani
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	Sharon	Ryan	Scotland Cancer		
	Simon	Stapley	Centre	Tausa	A la alvella la
	Elizabeth	Tee	-	Tareq	Abdullah
	Lenka	Zvirinska	-	Ghada	Al-Salih
inderfields	lva	Damyanova (PI)	-	Martin	Ball
Hospital			-	Karen	Bell Charlick
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	Darren	Gomersall	_	Fiona	McQueen
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Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
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	Kirsteen	Stuart		Angie	Cheyne
	Rasheed	Syed		Michael	Christie
	Ashita	Waterston		Kathryn	Connolly
	Cheryl	Wilson		Pat	Cooper
Sbyty Gwynedd	Catherine	Bale (PI)		Amber	Johnson
	Kelly	Andrews		Susan	Martin
	Naomi	Boyle		Celia	Meneses
	Claire	Fuller		Graeme	Murray
	John	Grant		Nicola	Price
	Emma	Hall		Sue	Rodwell
	Anna	Mullard		Mhairi	Scott
	Wendy	Saxton		Margaret	Smith
	Nick	Stuart		Bartosz	Was
	Alice	Thomas		Mehmood	Zaidi
	Linzi	Williams		Ishtiaq	Zubairi
A/:the december Community	Rachel	Williams	Cheltenham General Hospital	Kim	Benstead (PI)
Withybush General Hospital	Sarah	Gwynne (PI)	<u> </u>	Jaqueline	Aberdeen
<u> </u>		Moe (PI)	-	Rehana	Bakawala
	Fawwaz	Arikat	-	Sarah	Beazer
	Denisa	Asandei	-	Colin	Binks
	Sandra	Evans	-	Lucy	Blake
	Eirianydd	Garrard	-	Bethan	Cartwright
	Sophie	Glynn-Williams		Samuel	Croly
	Colette	Griffiths	_	Lin	Crossley
	Rachel	Hughes	_	Rachel	Durrant
	Catherine	MacPhee	_	David	Farrugia
	John	Murphy		Janet	Forkes
	Kirsty	Pope		Emma	Gilbert
	Rocio	Riba		Fabrizio	Mauri
	Sally-Ann	Rolls		Elaine	Pratten
	Abigail	Taylor		Elisabeth	Read
	Carol	Thomas		Nick	Reed
	Helen	Thomas	-	Rachel	Sayers
	Vallipuram	Vigneswaran	-	Neil	Shepherd
Aberdeen Royal	Leslie	Samuel (PI)	-	Stephen	Shepherd
Infirmary				continued on following	a bada)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Jennifer	Smith		Emma	Robjohns
	Sarah	Stanley		Patrick	Sarsfield
	Catherine	Stuart-Grumbar		Ingrid	Seath
	Bilal	Торіа		Shirley	Todd
	Kate	Trigg-Hogarth		Jane	Thompson
Clatterbridge	Nasim	Ali (PI)	<del></del>	Fiona	Walters (nee Hall)
Centre for				Claire	Webb
Oncology	\\/asla	Artist		Julia	Weston
	Wesley		Southampton	Tim	Iveson (PI)
	Shaker	Abdallah	General Hospital		
	Alexandra	Bailey		Liane	Armstrong
	Danielle	Campbell		Andrew	Bateman
	Maggie	Cantrell		Adrian	Bateman
	Joanne	Cliff (nee Mooney)		Emma	Brown
	Thomas	Davies		Holly	Burton
	Helen	Flint		Tracey	Callen
	Amy	Ford		Bethany	Caruana
	Barbara	King		Caroline	Chau
	Ayman	Madi		Tracey	Day
	Samah	Massalha		Efe	Evbuomwan
	Laura	McAllister		Meg	Gale
	Amir	Montazeri		Julie	Gwilt
	Joanne	Mullen		Sara	Hosseini-Moein
	Julie	O'Hagan		Alice	Johnson
	Anna	Olsson-Brown		Leah	Long
	Katharine	Pelton		Steve	McKenzie
	Kelly	Richardson		Charlotte	Rees
	Sandra	Robinson		Rasha	Said
	Joseph	Sacco	University College	John	Bridgewater (PI)
	Sarah	Stuart	Hospital		
	Hollie	Wilson	-	Adrienne	Abioye
	Pembe	Yesildag		Mahfuja	Ahmed
	Mariah	Zavery		Shamima	Akther
Royal Devon and	Melanie	Osborne (PI)		Maise	Al Bakir
Exeter Hospital	12			Adelaide	Austin
	Kizzy	Baines		Holly	Baker
	Tamika	Chapter		Jaytee	Barnett
	Elizabeth	Davey		Nina	Bason
	Susan	Downer		Isabelle	Brown
	Dawn	Edwards		Alexa	Childs
	Theresa	Lawless		Louise	Coyle
	James	Leavy		Patricia	Danaswamy
	Mark	Napier		Kanishka	Dissansayke
	(continued in next co	lumn)	((	continued on followin	g page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

lospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Rosina	Donovan		Paula	Botham
	Lola	Enemuwe		June	Carr
	Victor	Eneh		Louise	Devlin
	Gabrielle	Gould		Katie	Douglas
	Todd	Gumbleton		Grainne	Dunn
	Selina	Gurung		Mohammed	El-Abdullah
	Gemma	Hector		Lynn	Glass
	Sonya	Hessey		Kirsteen	Hamill
	Daniel	Hochhauser		Susan	Hastings
	Sabrina	Holohan		Rebecca	Heron
	Michelle	Hung		Chloe	MacDonald
	Georgios	Imseeh		Steven	Marshall
	Adoracion	Jayme		Laura	Miller
	Sarah	Kerr		Geradline	O'Dowd
	Khurum	Khan		Aqilah	Othman
	Jennifer	Laude		Diana	Park
	Xiao	Lu		Angela	Scullion
	Gina	Margai		Denise	Vigni
	Katie	Matthews		Kai	Yahya
	Eman	Mohamad	Charing Cross	Harpreet	Wasan (PI)
	Fatima	Mohamed	Hospital		
	Sam	Morris		Thalia	Afxentiou
	Anna	Nikopoulou		Riz	Ahmed
	Mayur	Patel		Melloney	Allnutt
	Maria	Power		Gareth	Barker
	Prakash	Rao		Abigail	Caldow
	Manuel	Rodriguez-Justo		Jolene	Carioni
	Derya	Sahin		Sarah	Chilcott-Burns
	Kai Keen	Shiu		Andrea	Davis-Cook
	Luke Owen	Steventon		Yomi	Fatola
	Mark	Sunga		Chee	Goh
	Hinesh	Tailor		Dorothy	Gujral
	Anisa	Tariq		Gillian	Hornzee
	Varji	Thayalan		Eleni	Josephides
	Jennifer	Thomas		Charlotte	Kelly
	Christopher	Wanstall		Daleep	Kumar
	Kristian	Warnes		Priya	Limbu
	Christopher	Whitton		Luzviminda	Llemit Ramos
	Georgina	Wood		Charles	Lowdell
onklands	Lisa	Rogers (PI)		Sophia	Magwaro
Hospital	2.00			Rochelle	McIntyre
	Anne	McKillop (PI)		Philippa	Nutkins
	Ashita	Waterston (PI)		Shola	Ogegbo

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principal investigator [PI])
	Anna	Osei-Kofi		Lai Mun	Wang
	Susan	Ramsey		Andrew	Weaver
	Pippa	Riddle		Sandie	Wellman
	Amalia	Saucan		Anthony	Wilson
	Helen	Saxby		Rebecca	Wiltshire
	Chantelle	Simpson		Martha	Woodward
	Aspa	Spyrou		Kirsten	Wynn
	Kirsty	Tunna	Leicester Royal	Anne	Thomas (PI)
	Iman	Yahya	Infirmary		
	Adrian	Zebrowski		Will	Steward (PI)
hurchill Hospital,	Tim	Maughan (PI)		Elizabeth	Andrzejewski
Oxford				Tracey	Alexander
	David	Badcock		Sarah	Attridge
	Magdalena	Benysek		Julie	Barlow
	Rosita	Broderick		Theresa	Beaver
	Anne	Butterfield		Amy	Branson
	Evelyn	Chan		Meera	Chauhan
	Philip	Charlton		Aurora	Del Pozo
	David	Church		Hadia	Haque
	Richard	Cousins		Hannah	Holdsworth
	Louise	Cowen		Rahima	Ibrahim
	Joanne	Davies		Chinenye	lwuji
	Steven	Davis		Mohammed	Karolia
	Alfonso	Gonzalez Blas		Lydianne	Lock
	Will	Goodman		Mohammed	Mahgoub
	Nikki	Hayward	·	Adrian	Nicholson
	Clare	Jacobs	·	Ahmed	Osman
	Patrycja	Jastrzebska	•	Katherine	Perkins
	Evanthia	Komninidou	'	Sarah	Porter
	Jonathan	Lau		Thiaghrajon	Sridhar
	Carolina	Lepiato		Judith	Underwood
	Clare	Marken		Balaji	Varadhan
	Kerrie	Marston		Julia	Walker
	Mark	Middleton		Kevin	West
	Ann	Murphy		Joanna	Wood
	Rebecca	Muirhead	Raigmore Hospital	Walter	Mmeka (PI)
	Adrian	Nicholson		Anglise	Addison
	Robin	Peach-Toon		Seonaid	Arnott
	Navin	Pol		Karen	Callum
	Sally	Rich		Denise	Campbell
	Nicola	Stoner		Fiona	Campbell
	James	Wakelin		Kay	Kelly
	(continued in next co			continued on following	-

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

lospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (princip investigator [PI]
	Alison	Macdonald		Michelle	Tingley
	Angela	Macgregor		Linzi	Wilson
	Carol	Macgregor		John	Bridgewater (PI)
	Zoe	Maciver	Hospital (Harlow)		
	Laura	Maclennan		Gemma	Cook
	Jude	Madeleine		Amelia	Daniel
	Melanie	McIlroy		Venkatesh	Gajapathy
	Mary	McKenzie		Evelyn	Holmes
	Neil	McPhail		Tayo	Jaiyesimi
	Alison	Nicholls		Joanne	Kellaway
	Marion	Paterson		Teresa	Light
	Leslie	Samuel		Lucinda	Melcher
	Georgina	Simpson		Cait	Rees
	Glenda	Sinclair		Vasi	Sundaresan
	Feng Yi	Soh	Royal Surrey	Tony	Dhillon (PI)
	Grant	Stenhouse	County Hospital		
	Joan	Stewart	-	Mazhar	Ajaz
	Una	Taylor	-	Nawa	Amin
	Zoe	Urguhart		Humyraa	Aziz -
ictoria Hospital	Sally	Clive (PI)		Izhar	Bagwan
(Kirkcaldy)	,			Catherine	Blake
	Brian	Adamson		Fiona	Butler
	Julie	Aitken		Penny	Champion
	John	Brush		Karen	Chan
	Rebecca	Cain	-	Sebastian	Cummins
	Lesley	Cargill		Tineke	Edmunds
	Shona	Cheyne		Sharadah	Essapen
	Clare	Cliff		Andrew	Furness
	Hazel	Cree		Laura	Gordon
	Karen	Gray		Di	Grainger
	Sophie	lwanikiw		Helen	Graves
	Fiona	Johnston		Imogen	Heenan
	Alastair	Matthews		Kirsty	Horwood
	Wendy	McCorry		Daniel	Jennings
	Catriona	Mclean		Natasha	Kamboh
	Fiona	Murdoch		Aga	Kehinde
	Ibrahim	Nawroz		Karla	Lee
	Julie	Penman		Sibylle	Lintott
	Anna	Scott		Gaybrielle	Livingstone
	Maria	Simpson		Cheryl	Marriott
	Deepak	Subedi		Catherine	Medcalf
	Jennifer	Tait		Aruna	Medisetti
	(continued in next co			Mahomed	Moosa

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Gayathri	Nagarajan		Deborah	Abrams
	Sarah	Oakes		Debbie	Austin
	Sue	Sargent		Carlos	Gonzalez
	Alexandra	Stewart		Matthew	Howlett
	Hasina	Thandar		Natalie	Lloyd
	Claire	Thompson		Rita	Ng
	Katharine	Webb		Paul	Ridley
	Rosalyne	Westley		Kirubah	Selvaraj
	Julia	Whittle		Liz	Sherwin
	Julie	Wilkinson		Bamini	Sivarajah
	Rebecca	Wills		Susan	Upson
t Helens Hospital	Zahed	Khan (PI)		Angharad	Williams
	Rachel	Cassidy		Jason	Wong
	Jenny	Cotton	Royal Hampshire	Luke	Nolan (PI)
	Lisa	Dobson	County Hospital		
	Nicola	Hornby		Louise	Beattie
	Sheila	Kelly		Julie	Conti
	Amanda	McCairn		Duncan	Cooke
	Jeanette	Ribton		Victoria	Corner
	Michelle	Robinson		Adrienn	Fazekasne Fulep
	Carol	Ross		Angela	Frith
	Victoria	Thomas		Julie	Gwilt
hesterfield Royal	Vanessa	Wilshaw (PI)		Samantha	Hammond
Hospital	<u></u>	<u> </u>		Liz	Happle
	Ibrahim	Al-Modaris		Lesley	Hollister
	Rebecca	Clark		Roger	Hudson
	Aurora	Del Pozo		Abigail	Hughes
	Alice	Dewdney		Lauriane	Kerwood
	Nicky	Ford		Matthew	Pitt
	Rachel	Gascoyne		Balvinder	Shoker
	Neeta	Gogna		Rao	Vuyyuru
	Charlotte	Hoult	Peterborough City	Catherine	Jephcott (PI)
	Emma	Hudson	Hospital		
	Kelly	Pritchard		Terri-Anne	Baker
	Martin	Shepherd		Helen	Bowyer
	Lesley	Stevenson		Kerrie	Cavanagh
	Danesh	Taraporewalla		Rebecca	Chilvers
	Julie	Toms		Marilyna	Chong
	Katie	Wallace		Laura	Costello
	Julie	Whitehead		Abigail	Hollingdale
	Lucinda	Wilson		Steph	Lawrence
swich Hospital	Gopalakrishnan	Srinivasan (PI)		Heather	Maccoll
	Zoltan	Szucs (PI)		Carla	Martino
(	continued in next co	lumn)	(0	continued on following	g page)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Surname (principal

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	investigator [PI]
эрни	Claire	Palombo		Julie	Froud
	Stuart	Richmond		Bojidar	Goranov
	Richard	Skells		Irene	Harvey
	Laura	Simon		Maggie	Kalita
	Claire	Snowden		Sarah	Kingdon
	Lisa	Wilde		Mike	Marner
	Louise	Wilmer		Laura	Marks
Calderdale Royal	Jo	Dent (PI)		Susan	McFarlane
Hospital	J0	Deni (Fi)		Chelsea	Morton
	Mohammad Irfan	Alam		Anna	Mucha
	Nick	Brown		Sarah	Prance
	Nicky	Daker		Olivia	Reed-Poysden
	Sam	Dale		Peter	Sankey
	Denise	Hancock		Helen	Smith
	James	Harris	Macclesfield	Victoria	Lavin (PI)
	Lisa	Horner	District General Hospital		
	Jeremy	Hyde	· ·	Ganesh	Radhakrishna (PI
	Rebecca	Jenkins		Catherine	McBain (PI)
	Christopher	Knight		Victoria	Adinkra
	Mandy	Madigan		Dane	Bradwell
	Adam	Mawer		Lisa	Brookes
	Belinda	McLean		Helen	Burns
	Sabiha	Ravat		Nicola	Dawson
	Hannah	Riley		Catherine	Fenson
	Jodie	Rowan		Lisa	Hardstaff
	Simone Deborah	Ryan		Abbi	Henderson
	Lisa	Shaw		Christy	Henderson
	Selina	Shaw		Pippa	Hill
	Kathryn	Smith		Debra	Jowle
	Christine	Turner		Mark	Lawrence
	Georgina	Turner		Joanna	Longden
	Hayley	Webster		Nicola	Lunt
	Tracy	Wood		Marilyn	McCurrie
Derriford Hospital	David	Sherriff (PI)		Karen	Rotchell
	Rebecca	Aaron	-	Barbara	Townley
	Bridget	Aire		Helen	Wassall
	Baffour	Amo-Takyi	-	Julie	Whitehead
	Erin	Brennan	-	Lesley	Wilkinson
	Lucy	Cadmore		lain	Woodhouse
	Leonie	Eastlake	Torbay District	Nangi	Lo (PI)
	Laura	Evenden	General Hospital		
	Kay	Facey		Michele	Allison
	Olivia	Fraser	(0	continued on following	g page)

First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
Kenneth	Almedilla		Sarah	Clark
Emmie	Arbury		Joseph	Gallagher
Lauren	Blunt		Svitlana	lyevkova
Jo	Blurton		Rashmi	Jadon
Catherine	Brookman		Catherine	Jephcott
lan	Buley		Natalie	Jones
Shelley	Chamberlain		Hannah	Loveday
Stacey	Davies		Jane	Macdonald
Angela	Foulds		Betania	Mahler-Araujo
Meadow	Fisher-Crisp		Debra	Mansergh
Joanne	Garfield-Smith		Ultan	McDermott
Petra	Gee		Lindsay	Piper
Caera	Good		Amy	Strong
Hannah	Griffin	<del></del>	Catherine	Thorbinson
Andrew	Harford-Brown		Saji	Victor
Prithvi	Jampana		Naval	Vyse
Ingrid	Koehler	-	Amanda	Walker
Tyler	Lowe	-	Emma	Wong
Sally	Maddison	-	Zsuzsa	Zaborszky
Mitchell	McMillan	Guy's Hospital	Paul	Ross (PI)
Louise	Medley	(London)		
Lyn	Micklewright		Samantha	Barrett
Louise	Paatz		Eva	Batovska
Maeve	Pomeroy		Jessica	Brady
Helen	Randall		Maribel	Boyce
Fleur	Rogers		Laura	Camburn
Lorraine	Thornton		Lorna	Caplis
Christine	Tsang		Noan Minh	Chall
Elaine	Vandecandalaere		Jason	Chow
Sarah	Wright		Chi Yee	Chung
Hugo	Ford (PI)		Sophie	Clark
			Sarah	Cleary
Athar	Ahmad		Victoria	Donovan
Alexandra	Azevedo		Sandra	Esteban Moreno
Lesley	Bennett		Adrienn	Fazekasne Fulep
Elizabeth	Blake		Lucy	Featherstone
Mark	Bolton		Michael	Flanagan
Rebecca	Bradley		Laura	Green
Jane	Bushen		Sara	Hulf
Joanna	Calder		Arun	Karnad
Anita	Chhabra		Sara	Kazemzadeh
Kathy	Chin		Vevangaune	Ketjiperue
	Kenneth Emmie Lauren Jo Catherine lan Shelley Stacey Angela Meadow Joanne Petra Caera Hannah Andrew Prithvi Ingrid Tyler Sally Mitchell Louise Lyn Louise Maeve Helen Fleur Lorraine Christine Elaine Sarah Hugo Athar Alexandra Lesley Elizabeth Mark Rebecca Jane Joanna Anita	First Nameinvestigator [PI])KennethAlmedillaEmmieArburyLaurenBluntJoBlurtonCatherineBrookmanIanBuleyShelleyChamberlainStaceyDaviesAngelaFouldsMeadowFisher-CrispJoanneGarfield-SmithPetraGeeCaeraGoodHannahGriffinAndrewHarford-BrownPrithviJampanaIngridKoehlerTylerLoweSallyMaddisonMitchellMcMillanLouiseMedleyLynMicklewrightLouisePaatzMaevePomeroyHelenRandallFleurRogersLorraineThorntonChristineTsangElaineVandecandalaereSarahWrightHugoFord (PI)AtharAhmadAlexandraAzevedoLesleyBennettElizabethBlakeMarkBoltonRebeccaBradleyJaneBushenJoannaCalderAnitaChhabra	First Name investigator (PI) Hospital  Kenneth Almedilla  Emmie Arbury  Lauren Blunt  Jo Blurton  Catherine Brookman  Ian Buley  Shelley Chamberlain  Stacey Davies  Angela Foulds  Meadow Fisher-Crisp  Joanne Garfield-Smith  Petra Gee  Caera Good  Hannah Griffin  Andrew Harford-Brown  Prithvi Jampana  Ingrid Koehler  Tyler Lowe  Sally Maddison  Mitchell McMillan  Louise Medley  Lyn Micklewright  Louise Paatz  Maeve Pomeroy  Helen Randall  Fleur Rogers  Lorraine Thornton  Christine Tsang  Elaine Vandecandalaere  Sarah Wright  Hugo Ford (PI)  Ande Bushen  Joanna Calder  Anita Chhabra	First Nameinvestigator (PI)HospitalFirst NameEmmieArburyJosephLaurenBlurtSvitlanaJoBlurtonRashmiCatherineBrookmanCatherineIanBuleyNatalieShelleyChamberlainHannahStaceyDaviesJaneAngelaFouldsBetaniaMeadowFisher-CrispDebraJoanneGarfield-SmithUltanPetraGeeLindsayCaeraGoodArmyHannahGriffinCatherineAndrewHarford-BrownSajiPrithviJampanaNavalIngridKoehlerTylerTylerLoweEmmaSallyMaddisonZsuzsaMitchellMcMillanGuy's Hospital (London)PaulLouiseMedleyMedleyLynMicklewrightSamanthaLouisePaatzMaribelMaevePomeroyJessicaHelenRandallLorrainLornaChristineTsangLauraElaineVandecandalaereJasonSarahWrightSophieHugoFord (PI)SophieSarahHightAdriennAlharAhmadVictoriaAlexandraAzevedoSandraLesleyBennettLouyJaneBushenSaraJoannaCalderArunAnitaChiabra </td

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Choi Chin	Lau		Alistair	Ellis-Jones
	Nick	Maisey		Emma	Hall
	Simranjit	Mehta		Rachel	Hughes
	Ngozi	Muoneke		Ravi	Kodavatiganti
	Theodorah	Nago		Arwel	Lloyd
	Rita	Njoku		Bethan Wyn	Owen
	Vitalis	Nwokorie		Beryl	Roberts
	Temi	Olusi		Charley-Anne	Rutter
	Kishen	Patel		Jane	Stockport
	Amy	Quinn		Gemma	Szabo
	Catherine	Rogers		lan	Walker
	Hannah	Rush		Claire	Watkins
	Susie	Slater		Glesni	Williams
	Anita	Soma		Linzi	Williams
	Chara	Stavraka	Glan Clwyd	Simon	Gollins (PI)
	Harriet	Waine	Hospital		
	Sally	Walker		Elizabeth	Allan
St George's	Fiona	Lofts (PI)		Jill	Andrews
Hospital				Kelly	Andrews
(London)	Doraid	Alrifa		Lisa	Ashley
				Llinos	Davies
	Nia	Alsamarrai		Rachel	Davies
	Jason	Chow		Clair	Domeney
	Alice	Dainty		Sarah	Evans
	Lorette	Ffolkes		Emma	Hall
	Caroline	Finlayson		Jane	Heron
	Claire	Gilmartin		Ravi	Kodavatiganti
	Anne	Haldeos		Joanne	Lewis
	Sam	Hollingworth		Arwel	Lloyd
	Geoffrey	Howell		Carey	Macdonald-Smith
	Robert	Ingham		Claire	McGregor
	Kay	Laurent		Bethan Wyn	Owen
	Vitalis	Nwokorie		Tracy	Parry-Jones
	Antonio	Pesino		Fiona	Redmond
	Mark	Quarrell		Beryl	Roberts
	Agne	Sekmokaite		Charley-Anne	Rutter
	Jesusa	Toledo		Libby	Thackray
Wrexham Maelor Hospital	Simon	Gollins (PI)		lan	Walker
. Ioopital	Stacy	Ackerley		Jill	Westlake-Guy
	Ashraf	Alkhaldi		Linzi	Williams
	Kelly	Andrews		Stephanie	Wynne
	. 10113	7 11 101 1011 10		(continued on following	

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
James Cook University	Nick	Wadd (PI)	Royal Cornwall Hospital	Richard	Ellis (PI)
Hospital				Linda	Allsop
	Andrea	Boyce		Nicholas	Ashley
	Alison	Chilvers		Kerry	Atkinson
	Anthony	Donnelly		Nigel	Bailey
	Helen	Dunn		Thea	Barlow
	Vicky	Hanlon		Kayleigh	Bennett
	Charlotte	Jacobs		Carolyn	Brode
	Steven	Liggett		Thomas	Cornell
	Craig	Mower		Alexander	Dengler
	Lisa	Peacock		Emma	Duley
	Jacqueline	Richards		Sophia	Eloi
	Agnieszka	Skotnicka		Caroline	Goddard
	Danielle	Sweeney		Aaron	Gould
	Jane	Thompson		Anne	Griffiths
	Hans	Van der Voet		Karina	Harris
	Gill	Wheater		Peter	Helliwell
	David	Wilson		Claire	Hill
	Jason	Wong		Louise	Johns
Poole Hospital	Amelie	Harle (PI)		Tinnaya	King
	Tamas	Hickish (PI)		Samantha	Lomax
	Michael	Adrio		Kirsty	Maclean
	Maria	Alban		John	Madine
	Julian	Alexander		Joe	Mathew
	Lyn	Allen		John	McGrane
	Mary	Apps		Fiona	Minear
	Beth	Aubrey		Sharon	Moore
	Helen	Bradley		Anna	Oakes
	Savina	Elitova		Caroline	Parnell
	Daniel	Fielding		Kerena	Partridge
	Maxine	Flubacher		Sallyanne	Platt
	Deborah	Forster		Kirsty	Prout
	Melanie	Foster		William	Pynsent
	Louise	Heckford		Rebecca	Rogers
	Jill	Hobson		Jenifer	Row
	Hannah	James		Laura	Royle
	Min Yee	Lee		Johanna	Skewes
	Helen	Morling		David	Smith
	Victoria	Osborne		Darren	Snell
	Sharon	Power		Luke	Townley
	Victoria	True	Royal Free Hospital		Krell (PI)
	Craig	Vincent	Noyal Free Flospital	Astrid	Mayer (PI)
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Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Tahmin	Ahmed		Edwin	Cooper
	lan	Clark		Sarah	De Bruijn
	Jen	Fraser-Fish		David	Donaldson
	Roopinder	Gillmore		Tracey	Duckett
	Sara	Hamilton		Adam	Edwards
	Ben	Marks		Shirley	Fox
	Leah	Meaden		Karen	Flynn
	Aarti	Nandani		Michelle	Kotze
	Tesha	Suddason		Michaela	Nock
	Sharon	Thompson		Jess	Perry
	Elizabeth	Woodford		Lucy	Pippard
outh Tyneside District Hospital	Ashraf	Azzabi (PI)		Kerry	Rennie
District Frospitar	Amy	Burns		Amber	Rowsell
	Kumud	Jain		Rufus	Smith
	Judith	Moore		Lesley	Thomas
	Ruth	Tindle		Barbara	Williams-Yesson
t Bartholomew's	David	Propper (PI)	Lincoln County Hospital	Zuzana	Stokes (PI)
Hospital (London)				Antoinette	Adu
(London)	Waheeda	Abida		Suzanne	Archer
	Hayley	Blackgrove		Sarah	Bell
	Joanne	Chin-Aleong		Jayne	Borley
	Nikolaos	Diamantis		Sarah	Coombs
	Resmi	Jayachandran		Olesya	Francis
	Sumaiya	Kamora		Annette	Hilldrith
	Cheryl	Lawrence		Kathryn	Hoare
	Alia	Mahboob		Carol	Lockwood
	Juan	Navarro		Maryanne	Okubanjo
	Tanjil	Nawaz		Rhiannan	Pegg
	Pratistha	Panday		Manuel	Ruiz-Echarri
	Hannah	Payne		Thomas	Sheehan
	Stephen	Russell		Anuradha	Sheth
	Sarah	Slater		Andrew	Sloan
eovil District	Andrew	Allison (PI)		Caroline	Taylor
Hospital	Andrew	Allisori (F1)		Ruth	Thoy
	Erica	Beaumont (PI)		Alyson	Wilson
	Matthew	Sephton (PI)	Maidstone Hospital	Mark	Hill (PI)
	Joanna	Allison		Doraid	Alrifa
	Zenaida	Armstrong		Elizabeth	Angus
	Claire	Barron		Paulette	Basham
	Nigel	Beer		Lisa	Brown
	Kate	Beesley		Tracey	Chambers
	(continued in next co			Alison	Davison

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Jackie	Evans		Rosalind	Roberts
	Sanjina	Kathuria		Maria	Scott
	Samantha	Kestenbaum		Rafael	Silverman
	Tiana	Kordbacheh		Ananth	Sivanandan
	Satish	Kumar		Tania	Slater
	Barbara	LeBrocq		Anita	Stevenson
	Gemma	McCormick		Richard	Swinden
	Christos	Mikropoulos		Jackie	Worville
	lan	Pamphlett		Georgina	Walker
	Joanne	Patterson		Andrew	Wright
	Caroline	Rodger	Hinchingbrooke	Cheryl	Palmer (PI)
	Holly	Slater	Hospital		
	Charlotte	Stevens		Shilamba	Bramham
	Jeff	Summers		Sue	Donnelly
	Alicia	Synowiec		Simon	Duke
	Katy	Taylor		Vanessa	Goss
	Lisa	Tribe		Beverley	Haynes
Nottingham	Cristina	Lopez Escola (PI)		Rebecca	Lam
University				Elizabeth	Lee
Hospitals	D -			Sarah	Littlechild
	Rebecca	Ashton		Adam	McGeoch
	Suha	Atabani		Suzanne	Miller
	Alex	Blades		Agnieska	Osmanska
	Emma	Blades	North Middlesex	John	Bridgewater (PI)
	Lauren	Blackburn	Hospital		
	Pauline	Brookes	-	Ernesto	Balaguer-Ruiz
	Eliot	Chadwick		Girish	Bhome
	Caroline	Coulson		Moira	Durdy
	Michelle	Cunnell		Lorraine	Hurl
	James	Donworth		Shardul	Kulkarni
	Jade	Eggleton		Simranjit Kaur	Mehta
	Susan	Elliott		Lucinda	Melcher
	Joanne	Hobbs		Julia	Rees
	Shaymaa	Hosni		Jamila	Roehrig
	Laura	Kirk		Rahi	Shah
	Emma	Marshall		Chloe	Van Someren
	Balwir	Matharoo-Ball	Queen Alexandra Hospital	Ann	O'Callaghan (PI)
	Kayleigh	Mills	Ποοριται	Oluwatobi	Adeagbo
	Jamie	Mills		Suhail	Baluch
	Jeanette	Mulhurn		Kathy	Blight
	Karen	Newcombe		Sherilee	Cook
	Vanessa	Potter			
	Tin	Sang-Tsang		Heather	Cuell

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Tracey	Dobson		Sonya	Goriah
	Муа	Gyi		Praba	Gupta
	Antony	Higginson		Ann	Hewins
	Samuel Luke	Hill		John	Murphy
	Chloe	Holden		Zohra	Omar
	Tracey	Lee		Bryan	Phillips
	Jayne	McCartney		Meena	Raj
	Badrriyya	Mohamedali		Kelly	Reed
	Sethupathi	Muthuramalingam		Rocio	Riba
	Andras	Nagy	Royal Albert	Francisca Marti	Marti (PI)
	Eleanor	Taylor	Edward Infirmary		
	Mary	Wands		Elena	Takeuchi (PI)
	Robert	Williams		Jennifer	Cannon
	Carole	Wragg		Kate	Chilman
Weston General	Stephen	Falk (PI)		Shien	Chow
Hospital	· 			Louise	Devereaux
	Paola	Di Nardo (PI)		Alison	Doran
	Marjorie	Tomlinson		Diane	Forrest
	Kathy	Beard		Karen	Moss
	Sandra	Beech		Monica	Patel
	Hannah	Berry		Angela	Power
	Debbie	Coles		Wendy	Stevens
	Donna	Cotterill	Sunderland Royal	Ashraf	Azzabi (PI)
	Harvey	Dymond	Hospital		
	Symeon	Eleftheriadis		Hayley	Anderson
	Rajesh	Gamare		Rod	Beard
	Christine	Graham		Jane	Cole
	Serena	Hilman		Michelle	Edwards
	Sarah	Kidd		Adam	Hassani
	Denise	Leighton-Price		James	Henry
	Hugh	Lloyd-Jones		Vivienne	Hullock
	Andrew	McKendrick		Stephen	Laybourne
	Kathryn	Munday		Paula	Newton
	Vivienne	Pixton		Rachel	Pearson
	Glenn	Saunders		lan	Pedley
	Ed	Sheffield		lan	Pepley
	Dawn	Simmons		Melanie	Robertson
	Axel	Walther		Fiona	Wakinshaw
	Rachel	Warinton		Kathryn	Wright
	Tom	Wells	Basingstoke and	Charlotte	Rees (PI)
Glangwili General	Mau-Don	Phan (PI)	North Hampshire Hospital		
	Samantha	Coetzee		Louise	Beattie
	(continued in next co			ontinued on following	

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N=2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principal investigator [PI])
	Victoria	Corner		Shiv	Gayadeen
	Abigail	Edwards		Rob	Glynne-Jones
	Adrienn	Fazekasne Fulep		Marcia	Hall
	Angela	Frith		Rakhi	Jain
	Julie	Gwilt		Colleen	Murray
	Liz	Happle		Julie	Russell
	Roger	Hudson		Waqar	Saleem
	Andrew	Jackson		Anand	Sharma
	Lauriane	Kernwood		Margaret	Stone
	Lauriane	Kerwood		Harsha	Vara
	Kathryn	Leach	Queen Elizabeth	Gary	Middleton (PI)
	Emma	Magras	Hospital (Birmingham)		
	Asmat	Mustajab	(DITTIIIIIIIIII)	Sabia	Akhtar
	Christina	Narh		Amisha	
	Pennie	Porter			Desai
	Arun	Selvaraju		Colm	Forde
	Jackie	Smith		Kam	Gareja
	Claire	Williams		Sharon	Hackett
orth Valley Royal	Dawn	Storey (PI)		Sam	Hopkins (nee Poole
Hospital				Mary	Kotadia
	Joanne	Blackburn		Victoria	Kunene
	Stephanie	Brogan		Catherine	Prest
	Raj	Burgul		Helen	Preston
	Eilidh	Henderson		Donna	Smith
	Jane	Keddie		Phillipe	Taniere
	Linnet	McGeever	Queen's Hospital Burton	Manjusha	Keni (PI)
	Kaye	McIlvar	-	Ann	Adams
	David	McIntosh	-	Mosan	Ashraf
	Caroline	Mcleary		Jo	Burns
	Lynn	Prentice		Helen	Cox
	Annette	Riley		Katy	English
	Joanne	Robinson	-	Annette	Fleet
	Anne	Todd	-	Sarah	Hathaway-Lees
	Patricia	Turner	-	Elizabeth	Kemp
	Sally	Young		Hayley	Lewis
Mount Vernon Hospital	Mark	Harrison (PI)		Clare	Mewies
	Farhan	Ahmed		Jennifer	Moyes
	Nicola	Anyamene		James	Price
	Nicky	Barnes		Scott	Sanders
	Neel	Bhuva		Adrian	Smith
	Sam	Bosompem		Alison	Tilley
	Kari	Evans	(	continued on following	g page)

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
Russells Hall	Ankit	Jain (PI)		Julie	Turner
Hospital				Nia	Viney
	Simon	Grumett (PI)		Dawn	Withers
	Joann	Atkinson	University Hospital	Vanessa	Potter (PI)
	Daniel	Bull	Coventry		
	Donna	Cleal		Jason	Allen
	Lesley	Edwards		Senthil Kumar	Athmanathan
	Kath	Harrow		Rachel	Bazeley
	Stacey	Jennings		Susan	Bird
	Lucy	Kadiki		Yasmin	Brough
	Karen	Kanyi		Maggie	Brown
	Sally	Keates-Porter		Dannielle	Burgess
	Pek	Keng-Koh		Luanne	Carey
	Margaret	Marriott		Philippa	Clark
	Julie	Matthews		Peter	Correa
	Karen	McGarry		Kishore	Gopalakrishnan
	Vanessa	Moore		Cheryl	Hunter
	Andrew	Moores		Sian	Kempster
	Manesh	Patel		Mohammed	Khan
	Veena	Shinde		Fiona	McGurk
	Lucie	Smith		Jade	McKelvie
	Lucy	Smith		Lucy	Miller
	Angela	Watts		Sarah	O'Toole
Singleton Hospital	Sarah	Gwynne (PI)		Karandeepu	Pachoo
	Cristina	Lopez (PI)		Noor	Shaw
	Alya	Al-Affan		Laura	Stanley
	Philip	Bryant		Charlie-marie	Suddens
	Karen	Chesters		Rachel	Thompson
	Sharon	Davies		Maria	Truslove
	Jenna	Edwards		Linda	Wimbush
	Stuart	Evans		Jane	Wording
	Tracey	Ford	University Hospital	Madhavi	Adusumalli (PI)
	Ricky	Frazer	of North Tees		
	Judith	Gooding		David	Wilson (PI)
	Olivia	Hatcher		Alison	Chilvers
	Gillian	Jones		Helen	Dunn
	Lewis	Jones		Sarah	Essex
	Maung	Moe		Mohammad	Hegab
	Karen	Phillips		Hyder	Latif
	Euan	Pratt		Moira	Percival
	Alex	Richards		Sarah	Pitcairn
	Louise	Thomas		Lynda	Poole
		lumn)		Pam	Race

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Andrew	Sigsworth		Elizabeth	Reay
	Eleni Andriana	Trigka	·	Timothy	Simmons
	Helen	Wardle	_	Carole	Stobbart
	Bill	Wetherill	-	Jonathan	Stoddart
	Pauline	Leonard (PI)	-	Nichola	Waugh
Hospital			-	Hesther	Wilson
(London)	5		Leighton Hospital	Michael	Braun (PI)
	Rashidat	Adeniba		Vanessa	Adamson
	Dhili	Arul		Carole	Bennion
	Jonathan	Flor		Kim	Best
	Kavita	Kantilal		Leanne	Everall
	Xiao Lou	Lu		Julia	Gemmell
	Mulyati	Mohamed		Laura	Hanton
	Michelle	Saull		Christy	Henderson
	Nuray	Temiz		Adele	Hough
	Azmina	Verjee		Chris	
	Simon	Wan			Hough
Freeman Hospital,	Ashraf	Azzabi (PI)		Cyndy	Jackson
Newcastle	0 1			Taya	Jones
	Craig	Alderson		Tracy	Larcombe
	Chris	Barron		Carolyn	Mansfield
	Michelle	Borthwick		Emma	Margerum
	Julie	Burton		Julie	Meir
	Kay	Carson		Andrew	Ritchings
	Fiona	Chapman		Paul	Simcock
	Sarah	Cook		Sarah	Tinsley
	Fareeda	Coxon		Caroline	Walker
	Sue	Farrell	Ninewells Hospital, Dundee	Sharon	Armstrong (PI)
	Elaine	Greaves	- Dundee	Jennifer	Allison
	Ahmed	Hashmi	-		
	Amanda	Henderson		Rachael	Banks
	Kathryn	Hewitt		Anne	Black
	Ben	Hood	-	Louise	Brannan
	Thomas	Jarvis		Frank	Carey
	Irene	Jobson		Shona	Carson
	Najibah	Mahtab		Helen	Cumming
	Lesley	Naik		Debbie	Forbes
	Stephanie	Needham		Audrey	Lyall
	Gemma	O'Neill		AJ	Munro
	lan	Pedley		Moira	Rogers
	Sindhu	Ramamurthy		lan	Sanders
	Zarine	Razvi		Gail	Weir
	(continued in next co		Westmorland General Hospital	David	Eaton (PI)
				Rebecca	Anderson

Hospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principal investigator [PI])
	Syed	Asghar		Richard	Osborne (PI)
	Manal	Atwan		Pauline	Ashcroft
	Claire	Bartlett		Corrado	d'Arrigo
	Ashoke	Biswas		Maxine	Flubacher
	Jennifer	Bowler		Jackie	Gibbins
	Karen	Burns		Karen	Hogben
	Rebecca	Calvert		Arabis	Oglesby
	Amy	Ford		Andrew	Rees
	Laura	Healey		Simon	Wilsher
	Nima	Herlekar	Great Western	Sarah	Lowndes (PI)
	Maria	Kassi	Hospital		
	Lauren	Kilifin		Graham	Brown
	Jo	Kilkenny		Christopher	Clarke
	Nicola	Mackenzie		Amanda	Colston
	Aileen	Menzies		Jan	Dodge
	Helen	Morris		Eva	Fraile
	Debbie	Power		Sarah	Grayland
	Jane	Ritchie		Lesley	Haxton
	Mary	Robinson		Lawrence	John
	Vickie	Rose	-	Jean	Kordula
	Rachel	Simmons		Lynsey	Kyeremeh
	Andrew	Taylor		Donna	Lake
	Hilary	Thatcher		Catherine	Lewis Clarke
	Gail	Wiley		Sarah	Long
elfast City Hospital	Victoria	Coyle (PI)		Dorota	Marciniak
	Conal	Askin		Laura	McCafferty
	Ellen	Brown		Darren	McFadden
	Karen	Campfield		Sue	Meakin
	Catherine	Davidson		Chanelle	Meyer
	Michael	Hanna		Tim	Owen
	Diane	Law		Cerila	Parajes
	Alison	McKeever		Ronak	Patel
	Aine	McKeown		Suzannah	Pegler
	Damian	McManus		Caroline	Pensotti
	Linda	McNeice		Joseph	Stevens
	Karen	Parsons	Milton Keynes University Hospital	Wasiru	Saka (PI)
	Miranda	Reid			
	Fiona	Tarpey	Поорна	Ann	Abraham
	Joanne	Todd		Hannah	Ansell
	Paul	Ward		Sam	Bosompem
	Richard	Wilson		Matthew	Burnett
Oorset County	Amelie	Harle (PI)		Chris	Ford
Hospital	ATTORIO	riune (i i)		(continued on following	

lospital	First Name	Surname (principal investigator [PI])	Hospital	First Name	Surname (principa investigator [PI])
	Chloe	Green		Victoria	Knight
	Sara	Greig		Tara	Lawrence
	Penni	Hawkins		Beverley	Mashegede
	Chamene	Hicks		Helen	Palmer
	Aarzoo	llyas		Kerry	Pettitt
	Charity	Masvaure		Gunjan	Phalod
	Louise	Moran		Manuel	Ruiz-Echarri
	Mala	Nathvani		Gemma	Sankey
	Cheryl	Padilla-Harris		Thomas	Sheehan
	Vijay	Patel		Rebecca	Spencer
	Shahriar Mohammed	Reza		Kinga	Szymiczek
	Syed Azhar Javed	Rizvi		Isobel	Thomas
	Abby	Skillington	Rotherham District	Joanne	Hornbuckle (PI)
	Jeannette	Smith	General Hospital		
	Oliver	Spring		Matthew	Barnes
	Heather	Thomas		Sarah	Besley
	Stephanie	Thorp		Meredyth	Harris
	Valerie	Webb		Kath	Lowe
	Dona	Wingfield		Scott	Nicol
	Christopher	Woodard		Susan	Oakley
ew Cross Hospital	Simon	Grumett (PI)		Amy	Rees
	Syed	Asghar		Charlotte	Widdop
	Vanda	Carter	Royal	Tamas	Hickish (PI)
	Sandeep	Dhillon	Bournemouth Hospital		
	Anna	Grant	·	Jocelyn	Ablorde
	Clare	Hammond		Omolade	Bakarey
	Kelly	Kauldhar		Rachel	Bower
	Margaret	King		Zoe	Clark
	Christine	Kirk		Nicole	Davies
	Claire	Lomas		Alison	Hogan
	Manel	Mangalika		Stephanie	Jones
	Gurminder	Sahota		Tiffany	Joyce
	Elaine	Wylde		Maria	Lane
ilgrim Hospital	Zuzana	Stokes (PI)		Sharon	Megson
	Antoinette	Adu		Sandy	Pressdee
	Simon	Archer		Linda	Purandare
	Gloria	Barone		Taslima	Rabbi
	Jayne	Borley		Emma	Sharland
	Wendy	Deamer		Esther	Una Cidon
	Jo	Fletcher		Luke	Vamplew
	Matthew	Flook		Jasmin	Webb

Surname (principal Hospital First Name investigator [PI]) Royal Marsden lan Chau (PI) Hospital (London) Helen Breeze Clifton Shirley Saoirse Dolly Sandra Esteban Moreno Lucy Featherstone Shelby Hatt Blanka Hezelova Lee Alexander Hazel Lote Lizzie Love Nnenna Ngwu Isma Rana Gihan Ratnayake Penny Rogers Clare Saffery Anna Scott Izelle Ueckermann Chloe Westrip Chau lan Abdelmalik Sally Gayahri Anandappa Joo Ern Ang Thushasa Ansari Sheila Azaiji-Benjamin Annette Bryant Shirley Clifton Richard Crux Cunningham David Diffley Sara Julie Duncan Laurice Edwards Sandra Esteban Moreno Featherstone Lucy Monika Ferencova Angela Gillbanks Kaur Sarnjeet Naila Kaudeer Shelize Khakoo Shannon Kidd Retchel Lazaro Alcausi (continued in next column)

Participating Hospitals in Descending Order of the Number of Patients Registered With All Staff Listed (N = 2,076) (continued)

Hospital	First Name	Surname (principal investigator [PI])	
	Hazel	Lote	
	Jacqueline	Oates	
	Bijal	Patel	
	Minal	Patel	
	Brenda	Pem	
	Sijy	Pillai	
	Clare	Saffery	
	Francesco	Sclafani	
	Gillian	Smith	
	Eleanor	Temple	
	Jan	Thomas	
	Andrea	Turner	
	Izelle	Ueckermann	
	David	Watkins	