

## ADVANCE:

**A COMMUNITY-BASED POINT OF CARE  
WHITE CELL COUNT DEVICE TO IMPROVE  
CRITICAL CARE PATHWAYS FOR CANCER  
PATIENTS WITH SUSPECTED  
CHEMOTHERAPY RELATED  
NEUTROPENIC SEPSIS: A FEASIBILITY  
STUDY.**

**PROTOCOL VERSION 5.0**

**20<sup>TH</sup> JANUARY 2023**

<b>Sponsor:</b>	Velindre University NHS Trust Unit 2 Charnwood Court, Parc Nantgarw, Nantgarw, Cardiff, CF15 7QZ
<b>Sponsor ref:</b>	2018/VCC/078
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## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Centre for Trials Research (CTR) SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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<b>Institution: Velindre University NHS Trust</b>		
<b>Name and Position</b>	<b>Signature</b>	<b>Date 03/02/2023</b>
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<b>Name</b>	<b>Signature</b>	<b>Date 31/01/2023</b>
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**General Information** This protocol describes the ADVANCE clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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This protocol has been developed by the ADVANCE Trial Management Group (TMG).

For **all queries** please contact the ADVANCE team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigator.

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**Registration:**

**Registration**

To register a participant into the Work Package 1: Non-randomised device cohort study contact a Participating Site Lead detailed above following the timeframes and further details described in See section 9.5.

**Clinical queries:**

**Clinical queries**

[POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk)

All clinical queries will be directed to the most appropriate clinical person.

**Serious Adverse Events:**

**SAE reporting**

Where the adverse device event meets one of the serious categories, a SAE form should be completed by the responsible clinician and submitted to

[CTR-SAFETY@Cardiff.ac.uk](mailto:CTR-SAFETY@Cardiff.ac.uk)

within 24 hours of becoming aware of the event (See section 16 for more details).

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## Glossary of abbreviations

<b>AE</b>	Adverse Event
<b>AR</b>	Adverse Reaction
<b>CI</b>	Chief Investigator
<b>CBC</b>	Cell blood count
<b>Chemotherapy</b>	Treatment with drugs that destroy malignant cells and tissue
<b>CRF</b>	Case Report Form
<b>CML</b>	Chronic Myeloid Leukaemia
<b>CTR</b>	Centre for Trials Research
<b>EG</b>	Executive Group (combined IDMC and TSC)
<b>FBC</b>	Full blood count
<b>GCP</b>	Good Clinical Practice
<b>GP</b>	General Practitioner
<b>HCRW PCU</b>	Health and Care Research Wales Permissions Co-ordinating Unit)
	Informed consent form
<b>ICF</b>	Informed Consent Form
<b>IDMC</b>	Independent Data Monitoring Committee
<b>ISF</b>	Investigator Site File
<b>ISRCTN</b>	International Standard Randomised Controlled Trial Number
<b>Lancet</b>	HTL-Strefa S.A. Prolance Max Flow Lancet. A CE marked medical device that will be used for the it's intended purpose of collecting blood.
<b>MASCC</b>	Multinational Association for Supportive Care in Cancer
<b>MASCC Index Score</b>	A score assigned using the MASCC risk index
<b>MCPCRC</b>	Marie Curie Palliative Care Research Centre
<b>MORE</b>	Manufacturer's On-line Reporting Environment (MORE). A electronic Vigilance report system for device manufacturers and suppliers and their authorised representatives.
<b>NHS</b>	National Health Service
<b>NICE</b>	National Institute for Clinical Excellence
<b>Non-CTIMP</b>	A study or trial that does not involve an investigational medicinal product
<b>OLO SYSTEM</b>	OLO CBC Analyser System comprising the OLO-U1 Analyser scanning and analysing device and CBC test kit. A CE marked <i>in vitro</i> diagnostic scanning and analysing device that will be used in this study for the it's intended purpose to screen capillary or venous whole blood samples to provide a 19-part CBC including a 5-part WBC differential and platelet count.
<b>Paclociclib</b>	A targeted (biological) therapy also known as Ibrance
<b>PI</b>	Principal Investigator
<b>PIS</b>	Participant Information Sheet
<b>POC</b>	Point of care
<b>POCT</b>	Point of care test
<b>QC</b>	Quality control
<b>R&amp;D</b>	Research and Development
<b>REC</b>	Research Ethics Committee
<b>SACT</b>	Systemic anti-cancer therapy
<b>SAE</b>	Serious Adverse Event
<b>SHO</b>	Senior House Officer
<b>SIGHT</b>	Sight Diagnostics UK Ltd
<b>SOP</b>	Standard Operating Procedure
<b>TMF</b>	Trial Master File
<b>TMG</b>	Trial Management Group
<b>TCS</b>	Transforming cancer services

<b>TSC</b>	Trial Steering Committee
<b>SUSAR</b>	Unexpected serious adverse event
<b>UKONS</b>	UK Oncology Nursing Society
<b>VCC</b>	Velindre Cancer Centre, the participating hospital site
<b>VPLG</b>	Velindre Patient Liaison Group
<b>WBC</b>	White blood cell
<b>WP</b>	Work package
<b>Yellow Card Scheme</b>	An electronic MHRA reporting scheme that collects information on suspected problems and incidents in the UK involving healthcare products to ensure they acceptably safe for patients and those that use them.

## 1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Summary of changes made since previous version
N/A	1.0 27/08/2019	First authorised version
1	2.1 22/10/2020	Amendment to address COVID impact
2	3.0 26/04/2021	<p>Amendment to address:</p> <ul style="list-style-type: none"> <li>• Change of device from Hemocue System to OLO System</li> <li>• Change of device manufacturer/supplier from Hemocue/Radiometer to Sight Diagnostics UK Ltd</li> <li>• Addition of option to collect an aliquot of the routine venous blood sample to use as a study sample to test for condition under investigation in WP1 cohort 2 instead of a new finger prick study blood sample</li> <li>• Addition of patients receiving paclociclib to WP1 Cohort 1 eligibility criteria</li> <li>• Further minor changes to address COVID impact</li> <li>• Amendment of statistics and endpoints in line with device change</li> <li>• Minor typographical errors</li> <li>• Change of key personnel</li> </ul>
3	4.0 14/09/2021	<p>Amendment to address:</p> <ul style="list-style-type: none"> <li>• Change of PI from Dr Amy Case to Dr Jennifer Kahan from 18/08/2021 onwards</li> <li>• Inclusion of option to use an additional finger prick sample and/or aliquot of the routinely collected venous blood sample as the 'study' sample for participants recruited to WP1 Cohorts 1.</li> </ul>

		<ul style="list-style-type: none"> <li>• Addition of option for participating site to use routinely collected patient email address to issue WP1 Cohort 2 PIS/ICF to participant due to changes in routine patient management processes.</li> <li>• Amendment of the permitted 1 hour for WP1 Cohort 1 and 2 participants to read PIS/ICF to 'adequate time' to avoid disruption to routine patient management procedures.</li> <li>• Change of source of finger prick lancet source to include external source.</li> <li>• Minor typographical errors</li> <li>• Change of key personnel</li> </ul>
5	5.0 20.01.2023	<p>Amendments to address:</p> <ul style="list-style-type: none"> <li>• Addition of a new arm (WP1 Cohort 3) to support survey implementation and additions to allow recruitment of broader category of patients to participate in this survey</li> <li>• Addition of WP1 anonymous survey collected under implied consent and as developed in collaboration with Velindre Patient Liaison group</li> <li>• Change in local PI at sole participating site</li> <li>• Minor typographical errors</li> </ul>

## 2 Synopsis

<b>Short title</b>	A point of care feasibility study to improve critical care pathways for chemotherapy-related sepsis.
<b>Acronym</b>	ADVANCE
<b>Development phase</b>	Feasibility
<b>CTR Portfolio Number:</b>	746
<b>IRAS Number:</b>	252236
<b>ISRCTN:</b>	TBA
<b>Funder and reference</b>	Tenovus - TIG2017-13
<b>Funder and reference</b>	Velindre Charitable Funds - 2018/18
<b>Funder and reference</b>	Sight Diagnostics UK
<b>Trial design</b>	Non-randomised cohort medical device feasibility study
<b>Population</b>	Cancer patients who present with suspected neutropenic sepsis whilst receiving chemotherapy
<b>Investigational device</b>	OLO-U1 System () (Sight Diagnostics UK Ltd).
<b>Comparator device</b>	Local high throughput lab-based device used to analyse 5 part white cell count
<b>Trial participants</b>	<p>WP1 Cohort 1: Cancer patients who present with suspected neutropenic sepsis whilst receiving chemotherapy</p> <p>WP1 Cohort 2: Cancer patients who require repeat Full blood count prior to SACT (systemic anti-cancer therapy) ie presented with borderline neutropenia at pre-chemotherapy assessment and require re-testing the day before, or on day of, planned chemotherapy, or will be receiving palbociclib (Ibrance) therapy.</p> <p>WP1 Cohort 3: Cancer patients receiving or who have received cytotoxic chemotherapy or radiotherapy</p> <p>WP2: Cancer patients and carers of cancer patients</p> <p>WP3: Healthcare workers</p>
<b>Planned sample size</b>	<p>WP1 Total: Approach 90, recruit 72, 65 valid test results.</p> <p>WP1 Cohort 1: Approach 60, recruit 48, 43 valid test results.</p> <p>WP2 Cohort 2: Approach 30, recruit 24, 22 valid test results.</p> <p>WP3 Cohort 3: Approach 24, 19 completed and returned surveys.</p> <p>WP2 : Approach up to 20. Recruit up to 10-15 participants.</p> <p>WP3: Approach up to 20. Recruit up to 10-15 participants.</p>
<b>Planned number of sites</b>	One – Velindre Cancer Centre (VCC), Cardiff, Wales
<b>Inclusion criteria</b>	<p>WP1 Cohort 1:</p> <ol style="list-style-type: none"> <li>1) 18 years old or over</li> <li>2) Received cytotoxic chemotherapy or radiotherapy within the last 6 weeks and has signs and symptoms or infection <u>and/or</u> a temperature &gt; 38°C or &lt; 36°C</li> <li>3) Admitted to any inpatient area at VCC for assessment for suspected neutropenic sepsis</li> </ol>

	<p>WP1 Cohort 2:</p> <ol style="list-style-type: none"> <li>1) 18 years old or over</li> <li>2) Patients requiring up to date white cell differential or platelet count immediately prior to therapy ie: Borderline neutropenia confirmed via a routine pre-chemotherapy whole blood neutrophil count, and require a repeat test either on the day of, or before, the next planned chemotherapy appointment or palbociclib therapy</li> </ol> <p>WP1 Cohort 3:</p> <ol style="list-style-type: none"> <li>1) 18 years old or over</li> <li>2) Cancer patients receiving or who have received cytotoxic chemotherapy or radiotherapy</li> </ol> <p>WP2:</p> <ol style="list-style-type: none"> <li>1) A member of the VPLG who is a current or previous cancer patient or a current or previous carer of a cancer patient</li> <li>2) 18 years old or over</li> </ol> <p>WP3:</p> <ol style="list-style-type: none"> <li>1) 18 years old or over</li> <li>2) Healthcare worker involved in the management pathway for neutropenic sepsis in cancer patients and/or medical device testing and/or implementation of new medical device at VCC and/or Velindre University NHS Trust</li> </ol>
<p><b>Exclusion criteria</b></p>	<p>WP1 Cohort 1:</p> <ol style="list-style-type: none"> <li>1) Has leukaemia.</li> <li>2) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).</li> </ol> <p>WP1 Cohort 2:</p> <ol style="list-style-type: none"> <li>1) Has leukaemia.</li> <li>2) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).</li> </ol> <p>WP1 Cohort 3:</p> <ol style="list-style-type: none"> <li>1) Has leukaemia.</li> <li>2) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).</li> </ol> <p>WP2:</p> <ol style="list-style-type: none"> <li>1) Considered by VPLG Co-ordinator or suitable delegate to be incapable of giving informed consent for any reason</li> </ol> <p>WP3:</p>

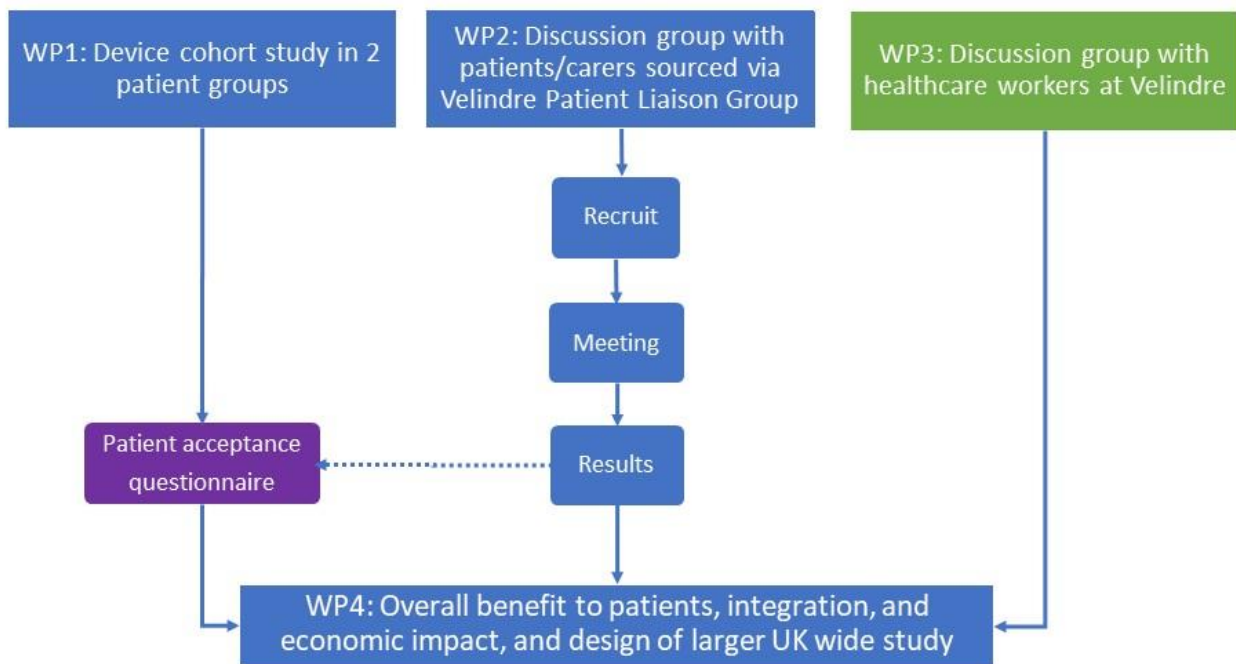
	1) Considered by Trial Manager or suitable delegate to be incapable of giving informed consent for any reason
<b>Comparator study duration</b>	WP1 Cohorts 1 and 2: 4 months from registration of first patient to end of patient follow-up inclusive of follow-up WP2 and 3: 1 month from issue of Participant Information Sheet (PIS)/Informed Consent Form (ICF) to date of group interview
<b>Comparator study follow-up duration</b>	WP1: 2-4 weeks following registration
<b>Planned trial period</b>	12 months
<b>Primary objective</b>	To clinically evaluate the investigational device (OLO System) versus the comparator standard laboratory device for the management of chemotherapy-related suspected neutropenic sepsis and pre-chemotherapy borderline neutropenia.
<b>Secondary objectives</b>	<ol style="list-style-type: none"> <li>1) To assess the feasibility of recruiting patients and use of the OLO System;</li> <li>2) To assess the safety of the OLO System in association with the UKONS Oncology/Heamatology 24 hour guidance and triage screening tool (Appendix 1) for patients who telephone for medical advice with suspected neutropenia and sepsis, to maximize both patient safety and independence;</li> <li>3) To assess patient and staff acceptability for the investigative device;</li> <li>4) To assess costs, including issues around hospital care/treatment and admissions.</li> <li>5) To assess which chemotherapy regimens are most likely to be associated with neutropenic sepsis and what current treatment management is;</li> <li>6) Through communication with key stakeholders and Welsh Government, explore the framework required to adequately inform the potential integration of the investigational device and triage questions into routine practice, within Wales and beyond;</li> <li>7) To design a larger UK-wide trial, in collaboration with patient representatives, to formally assess the investigational device for routine use within the NHS.</li> </ol>
<b>Primary outcomes</b>	Clinical evaluation of the OLO System: Neutrophil count from OLO (System and standard laboratory test full blood count (FBC).
<b>Secondary outcomes</b>	<ol style="list-style-type: none"> <li>1) Feasibility of recruiting patients and use of the OLO (System.</li> <li>2) Acceptability of OLO (System to patients and staff</li> <li>3) Costs.</li> <li>4) Outcomes relating to UKONS data and prescription data routinely collected in hospital databases (e.g. CANISC/Chemocare).</li> <li>5) Integration of OLO System.</li> <li>6) Summaries of discussions and collation of integration issues.</li> <li>7) Design of a larger UK-wide trial.</li> <li>8) Draft protocol suitable for funding application process.</li> </ol>



### 3 Trial summary & schema

#### 3.1 Trial schema

Figure 1. Work package overview



**Figure 2. WP1 Device cohort study**

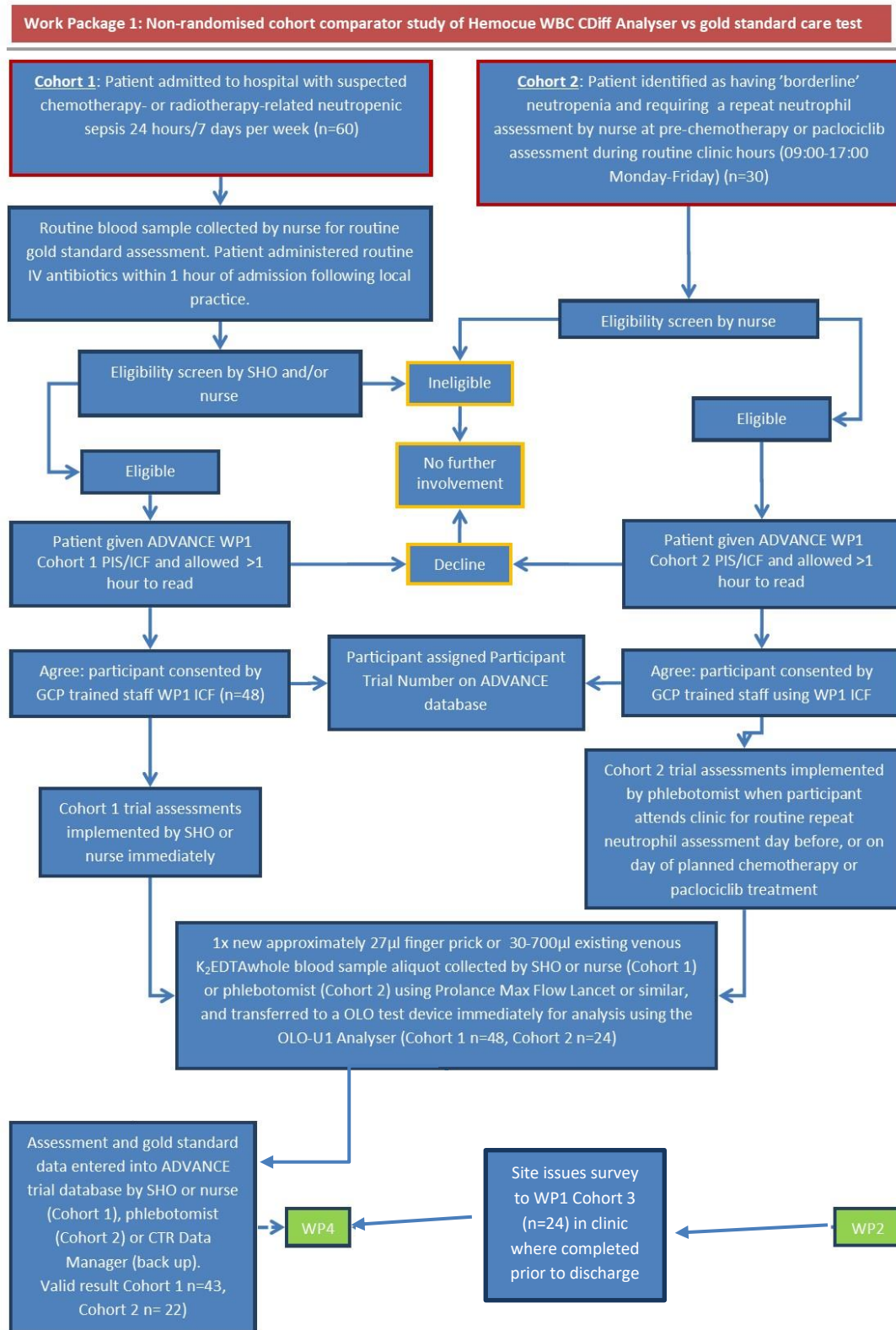
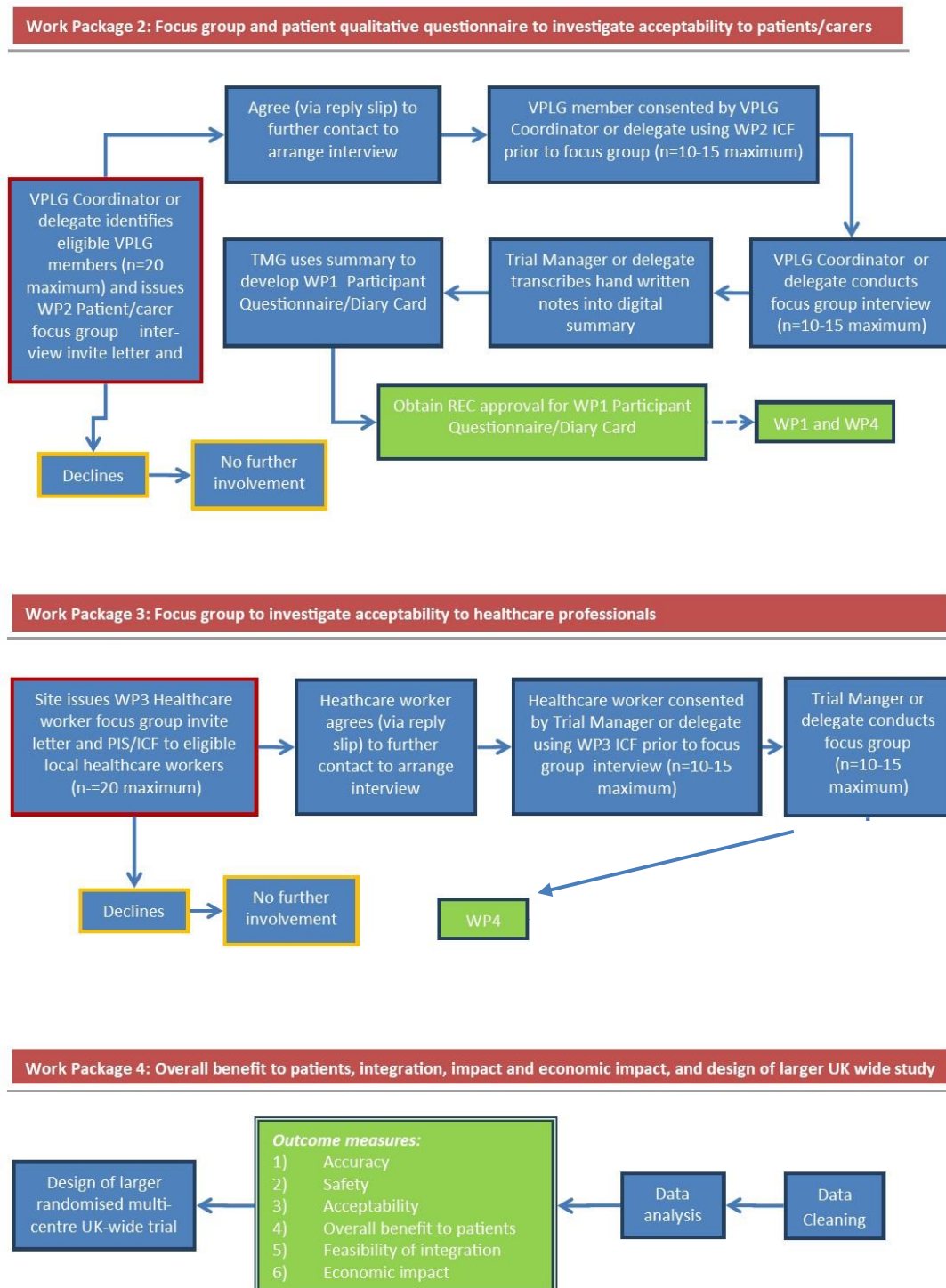


Figure 3. Qualitative research work packages



### 3.2 Trial lay summary

ADVANCE is a 12 months feasibility study aimed at improving pathways for cancer patients at risk of sepsis whilst receiving chemotherapy or palbociclib (Ibrance). Patients receiving these drugs as a part of their cancer treatment often have a lowered immunity and may be unable to fight off infections. This can mean that they are at risk of serious illness or death. The ability to monitor patients who have received hospital-based chemotherapy in their own home or other suitable location (for example, GP or Tenovus chemotherapy bus) may help more quickly identify those patients at high risk or minimal risk from neutropenic sepsis.

Following current UK NICE guidelines, UK cancer centres instruct patients on chemotherapy to take their temperature if they feel unwell, and to report this by telephone to the centre as soon as possible. These patients will be screened or triaged over the telephone and, if considered to have suspected sepsis due to lowered immunity (lowered white cells), attend hospital and undergo assessment including a routine blood test. If their blood test reveals that their anti-infection cells (white cells) are low they will need to stay in hospital to receive antibiotics as a drip treatment.

The same routine blood test is also used in a routine pre-chemotherapy safety assessment to determine if the patient is well enough to start or continue receiving each new cycle of chemotherapy.

We wish to test whether a new piece of equipment, the OLO CBC Analyser System (OLO System) System manufactured by Sight Diagnostics UK Ltd (Sight), which can perform this blood test in 10 minutes in the clinic using two drops of blood, can prevent patients from being admitted to hospital unnecessarily and/or delay of chemotherapy by ruling out a low white cell count.

This study will explore:

- 1) The accuracy and safety of using this system in the laboratory as an aid to the decision-making processes. We will test the device alongside the current routine laboratory blood test used to diagnose neutropenic sepsis in patients receiving chemotherapy. Patients will be recruited to two separate cohorts:
  - i) Acute admissions out of hours and weekends, supported by Senior House Officers and the nursing team;
  - ii) Pre-chemotherapy checks in patients presenting with borderline white cell counts prior to or on the planned date of chemotherapy, supported by phlebotomists.

Eligible participants will be asked to consent to this part of the study upon presentation at the hospital. We will test their blood using the routine laboratory method and the OLO System. We will use the

data to determine the accuracy and safety of the OLO System compared to the standard laboratory test.

2) The acceptability of using the OLO System to patients and their carers. We will conduct a discussion group meeting with cancer patients and their carers to identify appropriate acceptability issues, concerns, topics and questions. Attendees will be recruited via the Velindre Patient Liaison Group (VPLG) and Velindre Patient Experience Manager or a suitable delegate at VCC, Velindre University NHS Trust. Potential attendees will be given a participant information sheet (PIS) providing further information about the meeting and asked to provide written consent via an Informed Consent Form (ICF) and/or verbal consent prior to their participation. The meeting will be held in Cardiff or remotely online. The discussion will be recorded via hand-written notes documenting participants' responses. Notes will be summarised in digital format and used to design a participant survey that will be submitted for Research Ethics Committee (REC) approval. Patients recruited in part 1) above will then be asked to consent to complete the ethically approved survey. Their responses will be analysed to find out if replacing the standard laboratory test with the OLO (System is acceptable to patients and their carers.

3) The acceptability of using the OLO System to healthcare professionals. We will conduct a second discussion group meeting with health care professionals (for example, nurses, doctors, senior house officers, phlebotomists, etc.) who have been involved in the testing of the OLO System in 1) above. Potential attendees will be provided with a PIS providing further information about the meeting and asked to provide written consent via an Informed Consent Form (ICF) and/or verbal consent prior to their participation. The discussion will be recorded via hand-written notes and summarised in digital format. Participants' responses will be analysed to find out if replacing the standard laboratory test with the OLO System is acceptable to healthcare workers. Topic areas may include ease of use, accuracy, safety, impact on current patient management pathways and procedures, etc.

4) We will use the results of 1) to 3) above to determine the overall benefit to patients, including whether this equipment should be considered for routine use in patients receiving chemotherapy to improve patient choice, control and independence in relation to their illness. Also, to determine how this new approach can be integrated across the UK and the likely economic impact.

Ultimately, we aim to improve outcomes for patients receiving chemotherapy by:

- Preventing wasted journeys, inefficient contacts with the NHS and hospital admissions;
- Detecting low white blood count early to prevent life threatening complications;

- Provide reassurance and engagement in the management of patients' cancer.

The additional benefits to the health service may include:

- Avoiding unnecessary assessment of patients with an increased body temperature, but are otherwise well, in hospitals and cancer centres;
- Identifying patients who need urgent assessment, to improve on delivery times and reduction of risk.

The study will involve a diverse team of collaborators based in the UK at:

- The CTR, Cardiff University
- MCPCRC, Cardiff University
- Velindre University NHS Trust VPLG (Cardiff)
- Velindre University NHS Trust Innovation, Service Improvement, Information, Management and Technology, Education and Development, and Clinical Trials Groups (Cardiff)
- Cardiff and Vale University Health Board Point-of-Care Services and Haematology Groups (Cardiff)
- Sight, (manufacturer and sole UK distributor of the OLO System who will provide the equipment and reagents free of charge)

The study may also involve liaison with external UK Health Care bodies, including the UK Oncology Nursing Society (UKONS).

If the feasibility study is a success, we will develop a separately funded, larger clinical trial in which we will explore the use of the OLO System and assess the overall benefit to patients as well as the economic impact.

## **4 Background**

### **4.1 Rationale for current trial**

Annually, in the UK >200,000 people receive chemotherapy as a part of their cancer treatment [1]. Chemotherapy kills rapidly dividing cells; however, this includes white blood cells (WBC): the body's defence against infections. Chemotherapy is administered for a set period of days over a number of cycles to ensure the optimal balance of recovery and clinical outcome, e.g. 6 cycles of 21 days. Patients receive treatment in the hospital and return home to cope with the side effects.

Following chemotherapy up to 10% of patients will experience complications that lead to a hospital admission. It is believed that a significant proportion of these admissions could be avoided by

integrating recent technological advances. Recent data suggests that patients with cancer desire a greater input to their cancer care [2], with greater control. This work is consistent with the evidence developed by Velindre University NHS Trust on patient values (see Figure 1) and clearly has the potential to provide patient enabling strategies based on a platform for:

- Choice;
- Control;
- Communication;
- Information;
- Independence;
- Highest quality of care

**Figure 4.** Evidence developed by Velindre University NHS Trust on patient values



All of which are aligned to the principle of co-production between patients, health care teams and government; included in Prudent Healthcare.

One of the most significant complications relating to chemotherapy administration is neutropenic sepsis. This condition is variably defined internationally but within the UK usually refers to a patient with a temperature  $\geq 38^{\circ}\text{C}$ , or clinical signs/symptoms of infection, and an absolute neutrophil count

$\leq 0.5 \times 10^9/L$  (3). Neutropenic sepsis carries the risk of prolonged hospital admission and untimely death, if not dealt with as a medical emergency. Timely medical attention with intravenous fluids and empirical antibiotics can improve outcomes and ultimately prevent death. Kumar et al have previously identified that for every hour of delay in antibiotic administration the risk of death increases by 7.8% (4).

A significant component of patient education delivered by cancer centre staff in the UK prior to and following the delivery of chemotherapy, relates to a need for the patient to inform the specialist medical team if they experience any fever of  $\geq 38^\circ\text{C}$  or if they feel unwell (5).

The National Institute of clinical Excellence (NICE) issued clinical guidance in September 2012 [3] on the management of neutropenic sepsis and has identified key recommendations, including:

- Suspect neutropenic sepsis in patients receiving anti-cancer treatment who become unwell.
- Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.
- Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately.

This national review also identified areas in need of further research and development and recommended “a prospective study to be carried out to determine which signs and symptoms experienced by patients in the community predict neutropenic sepsis and the outcomes of these episodes”. This national review was reviewed in February 2014 and again in February 2019. Neither review identified major studies that will affect the recommendations in the following 3-5 years, i.e. before February 2022.

The ADVANCE trial might lead to improved triage of patients for appropriate interventions tailored to the individuals need in a risk stratified fashion.

Advances in care that result in a reduction in unnecessary hospital admissions for cancer patients have potential to save significant amounts of time and money within the National Health Service, meeting the principles of “prudent health care”.

The ability to monitor patients who have received hospital-based chemotherapy in their own home may help more rapidly identify patients at high risk or minimal risk from neutropenic sepsis. The technology now exists for point of care (PoC) testing to assess a patient’s white cell count indicating more effectively the risk of neutropenic sepsis, when they have a fever or feel unwell. This has the potential to improve the safety and care of our patients receiving chemotherapy. Early identification



of a low white cell count can lead to timely and potentially life-saving interventions. Conversely, identifying the patient who is adequately fighting an infection with a normal white cell count, may prevent inappropriate hospital admission and appropriate recovery at home. Monitoring patient status between doses of chemotherapy may also reduce the risk of calling patients in for treatment when they are insufficiently recovered from the previous cycle. In summary, regular monitoring may help improve patient care, patient quality of life and hospital efficiency, across Wales and beyond.

Assessing a patient's condition when they are not in the hospital is a significant challenge. Patients may find it difficult to separate expected effects of the chemotherapy from the symptoms of serious adverse effects. A PoC system empowers patients to be actively involved in the remote monitoring of their health whilst at home and to seek appropriate help and admission to hospital under the correct circumstances.

This project is part of a broader piece of work looking at transforming cancer services (TCS) within Wales [6].

## **4.2 Justification for trial design and investigational and comparator device choice**

### **4.2.1 Local audit**

An audit conducted at VCC in 2017 identified that 96 cancer patients with chemotherapy-related suspected neutropenic sepsis were admitted to VCC over a period of 3 months [7]. One third had confirmed neutropenic sepsis. Two thirds did not have neutropenia, a proportion of whom may have avoided admission if this feasibility and subsequent larger trial are successful. This pool of retrospective patient data has been used to inform the design of this feasibility study.

### **4.2.2. Device choice**

Traditionally, full blood counts (FBCs) have been analysed using large laboratory-based high throughput microplate or tube equipment such as the Horiba Pentra with an average vein to report time of 4 hours [8]. Recently the haematology point of care test (POCT) market has grown and a number of discipline-specific novel devices have been developed to analyse FBCs. Several analysers capable of 3-part differentials (neutrophils, eosinophils, and basophils grouped together to produce a total granulocyte count) are currently commercially available including POCH-100i (Sysmex Corporation, Kobe, Japan) and the ABX Micros series (Horiba Medical, Northampton, UK) OLO (Sight Diagnostics).

Neutrophil count is an important criterion to clinicians when making decisions about treatment of oncology patients. The availability of POCT analysers capable of producing an FBC with a 5-part differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils) is limited but includes the HemoScreen (PixCell Medical, Israel), the Yumizen H500 (Horiba Medical, Northampton, UK), and the OLO (Sight Diagnostics) System equipment

The Yumizen H500 is based on Horiba's Micros platform, is aimed at the point-of-care and primary care market, and has comparable accuracy to the Horiba Pentra 120 series [9]. The device can provide a result within 2 minutes and has both open and closed venous tube options, making it suitable for paediatric and capillary samples. The device has been evaluated for the improvement of point of care testing for paediatric patient groups and been found to have exceptional correlation with the Horiba Pentra DX120 by the Cardiff & Vale Health Board with an improved vein to report time of less than 15 minutes [10].

The OLO white cell differentiation kit also undertakes a 5 part white cell differentiation and also includes platelet count, the kit is in commercial use and will be evaluated locally through the work packages in this study. The technology uses an AI based camera based technology.

We are collaborating with Sight Diagnostics who are distributor and manufacturer of the OLO System. The equipment is CE marked for clinical use and has undergone testing to demonstrate that it can effectively report on a patients' total WBC count and five-part WBC differential count and platelet count ..

Compared to the Yumizen and Horiba systems the OLO kit is portable with a small footprint and weight costs less, and can be used with both venous blood samples and samples taken using the novel Microcuvette finger prick blood sample device. However, it has a lower throughput and longer time to result (11 minutes minimum). Despite these drawbacks, the system is potentially better suited than its 5-part differential competitors to niche remote locations in which a patient with suspected neutropenic sepsis may present, for example the inpatient hospital assessment unit, GP practice, and Tenovus chemotherapy bus.

The Sight OLO System has been evaluated against a variety of comparator systems in the public and private hospital sector, main and oncology lab environment, and adult and children hospital settings with comparable results [10-15].

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Patient centred values have been a key area of work within NHS Wales and include the desire for patients to have greater control over their treatment. We believe the OLOLO (Sight Diagnostics) system has the potential to offer this control. However, there remains a lot to do in this arena with respect to effective use, location of use (for example clinic, Tenovus bus, patient home), operator, and patient acceptance. Assessment is required in important sub-populations including the less technologically aware, less dextrous and frailer individuals.

## **5 Trial objectives/endpoints and outcome measures**

The proposal aims to investigate the most effective placement of the OLO (Sight Diagnostics) system. Dependent upon this evaluation it will lead to the submission of a funding request for a full scale randomised controlled trial within NHS cancer services, led by Wales.

### **5.1 Objectives**

To clinically evaluate the investigational device (OLO (System) versus the comparator standard laboratory device for the management of chemotherapy-related suspected neutropenic sepsis and pre-chemotherapy borderline neutropenia.

The secondary objectives of the study are:

1. To assess the feasibility of recruiting patients and use of the OLO (System);
2. To assess the safety of the OLO (Sight Diagnostics) System in association with the UKONS Oncology/Heamatology 24 hour guidance and triage screening tool (Appendix 1) for patients who telephone for medical advice with suspected neutropenia and sepsis, to maximize both patient safety and independence;
3. To assess patient and staff acceptability for the investigative device;
4. To assess costs, including issues around hospital care/treatment and admissions.
5. To assess which chemotherapy regimens are most likely to be associated with neutropenic sepsis and what current treatment management is;
6. Through communication with key stakeholders and Welsh Government, explore the framework required to adequately inform the potential integration of the investigational device and triage questions into routine practice, within Wales and beyond;
7. To design a larger UK-wide trial, in collaboration with patient representatives, to formally assess the investigational device for routine use within the NHS.

## 5.2 Primary outcomes measure(s)

### ***Clinical evaluation of the OLO (Sight Diagnostics) system:***

- Neutrophil count from OLO (Sight Diagnostics) system and standard laboratory test full blood count (FBC).

## 5.3 Secondary outcomes measure(s)

### ***Feasibility of recruiting patients and use of the OLO (Sight Diagnostics) system:***

- Proportion of those recruited from those consented and/or approached
- Proportion of recruited participants with a valid (as opposed to an invalid test result) from all recruited participants. A valid result is when the OLO system neutrophil result is  $\pm 0.2 \times 10^9/L$  of the laboratory gold standard result;
- Proportion of recruited participants returning the follow-up survey from all recruited participants;
- Number and type of OLO System (Sight Diagnostics) device flags and error codes raised during device operation for fingerprick versus venous blood sample to assess device accuracy;
- Number of re-takes of finger prick versus venous blood sample to assess device accuracy.
- Number of cases in which a discrepancy between the OLO System and gold standard would change the management of the patient, according to retrospective clinical review.
- Number of patients with valid OLO System test results for:
  - Haemoglobin – (validity  $\pm 0.7$  g/L)
  - Platelets – (validity  $\pm 15 \times 10^9/L$ )
  - Lymphocytes – (validity  $\pm 0.3 \times 10^9/L$ )

### ***Safety:***

- Sepsis-related mortality and morbidity. The number of patients diagnosed with sepsis.

### ***Acceptability of OLO (Sight Diagnostics) system to patients and staff:***

- Acceptability indicators collected via patient focus discussion group (feedback on draft qualitative survey, perceived benefits and disadvantages of the intervention, views around recruitment and/or randomisation in a future UK-wide study design);
- Number of healthcare workers recruited to healthcare worker discussion group meeting (from those invited).

- Number of healthcare workers recruited to healthcare worker discussion group meeting completion (from those screened).
- Acceptability indicators collected via healthcare worker focus group interview (preferred device operator, device placement and blood collection method, perceived benefits and disadvantages of the intervention, potential hurdles to implementation and impact on future UK-wide study).

**Costs:**

- In patients in which the OLO system result could have prevented unnecessary interventions, number of wasted journeys and unnecessary hospital admissions, bed occupancies, and assessments (negative OLO (Sight Diagnostics) system test results);
- Number of patients with increased body temperature, who are otherwise well, with a negative OLO result that would avoid unnecessary assessment of patients in hospitals and cancer centres; Number of detections of low white blood count early to prevent life threatening complications (positive OLO (Sight Diagnostics) System test results and data capturing time of patient in clinical system);
- Number of unnecessary delays in chemotherapy administration;
- Number of unnecessary antibiotic prescriptions;
- Number of inefficient contacts with the NHS and hospital admissions (via screening data of patients not admitted after triage but later found to have neutropenic sepsis);
- Ability of system to provide reassurance and engagement in the management of patients' cancer (indicators collected via patient/carer and healthcare worker focus group interviews).

***Chemotherapy regimens associated with sepsis and treatment management***

- Outcomes relating to UKONS data and prescription data routinely collected in hospital databases (e.g. CANISC/Chemocare).

***Integration of OLO (Sight Diagnostics) system***

- Summaries of discussions and collation of integration issues.

***Design of a larger UK-wide trial***

- Draft protocol suitable for funding application process

## **6 Trial design and setting**

ADVANCE is a non-randomised cohort medical device comparator feasibility study to investigate the ability, safety and acceptability of a community-based point-of-care medical device (the OLO (Sight Diagnostics) System) to improve the patient management pathway for chemotherapy-related suspected neutropenic sepsis. The work will be structured into four separate work packages (WP) as described below.

## 6.1 Work Package 1 (WP1): Cohort comparator study

This WP will identify the key components that may make the pilot and future trial safe and accurate for patients and will be led by the Trial Manager (TM) at the CTR, Cardiff University with support from the CI.

### 6.1.1 Cohort selection

A healthcare worker discussion group meeting held at VCC in April 2019 identified three local areas to explore for use of the OLO (Sight Diagnostics) System in the management of cancer patients:

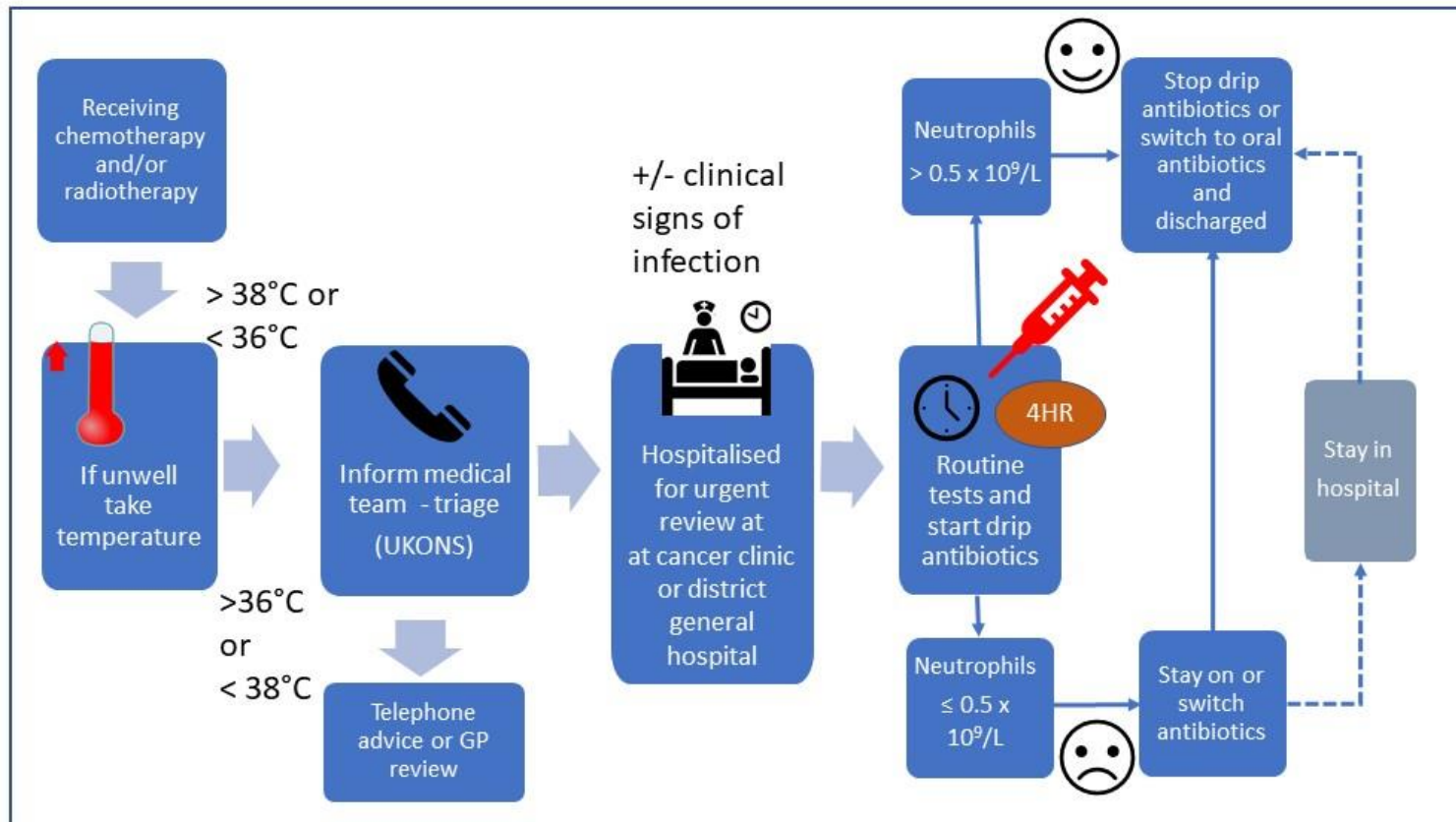
1. Acute admissions between 09:00 and 17:00, supported by Acute Nurse Practitioners and/or Acute Oncology Staff (AOS)
2. Acute admissions out of hours and weekend, supported by Senior Hours Officers (SHOs) and the nursing team
3. Pre-chemotherapy checks of patients who have presented with 'borderline' neutropenic (WBC counts) prior to or on the day of chemotherapy, supported by Phlebotomists.

The staff groups managing these areas vary dependent on whether the patient presents as an acute admission during normal working hours or out of hours and weekend. Similarly, the location of processing of whole blood samples collected during this process, and the gold standard equipment varies dependent on if the patient presents at clinic during or outside of routine local clinic and sample analysis hours. Routine samples collected from patients between 09:00 and 16:00 Monday to Friday will be analysed locally at the VCC Laboratory. Routine samples collected outside of these hours during the evening and/or weekend will be transported to the Cardiff & Vale Health Board Laboratory Service at a separate location (Heath Hospital site, Cardiff) for testing.

Taking these local aspects into account, the discussion group concluded that areas 2 and 3 were most likely to be deliverable locally with maximum impact due to limited availability of some staff groups and logistics of moving device equipment between different locations and teams. Therefore, this feasibility study will investigate two patient cohorts:

**Cohort 1: Suspected neutropenic sepsis:** Patients who, following UKONS assessment via telephone triage have been asked to attend the clinic for further assessment for suspected neutropenic sepsis, and present as an acute admission out of hours and at weekends (Figure 5)

**Figure 5.** Routine patient management pathway for suspected neutropenic sepsis in patients receiving chemotherapy





**Cohort 2:** ‘Borderline’ neutropenia: patients with an inconclusive ‘borderline’ neutrophil count at their pre-chemotherapy assessment who require a repeat test prior to receiving chemotherapy on the planned day of chemotherapy (Figure 6.).

Participants in both cohorts will be asked to consent to the provision of a new study blood sample collected via a CE marked finger prick medical device for analysis using the OLO (Sight Diagnostics) System. The results of the OLO (Sight Diagnostics) System will not be used to manage patients participating in either cohort.

**Cohort 3:** Patients attending Velindre Cancer Centre who are currently or have previously been receiving therapy that might cause a low white blood cell count or neutropenic sepsis. These patients will be asked to participate in the survey part of the study only.

#### **6.1.2 Investigational device**

Sight Diagnostics will supply two OLO Systems) for the purpose of this trial.

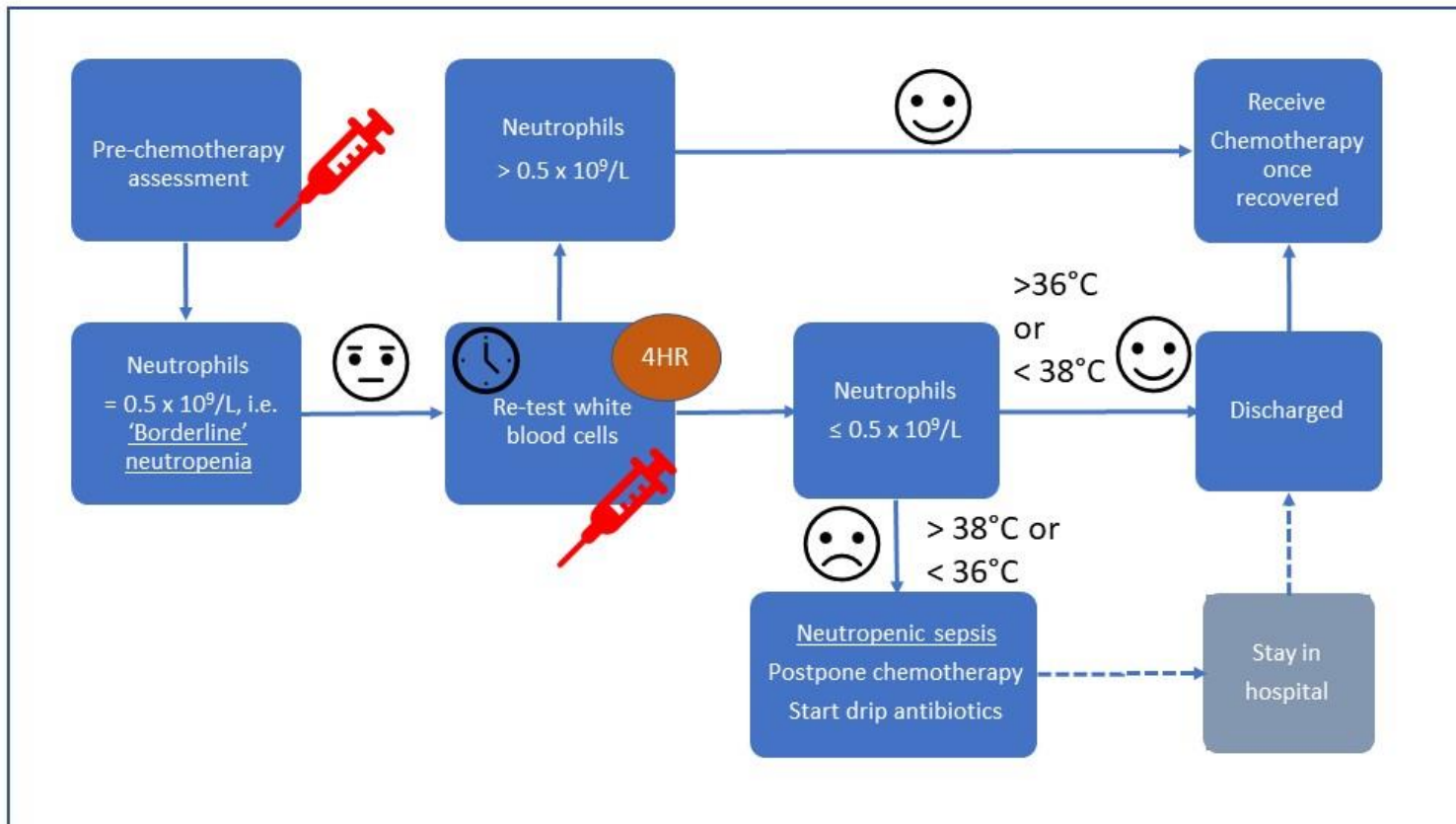
#### **6.1.3 Acceptability survey**

Participants in a third cohort (WP1 Cohort 3; n=24) will be given an anonymous survey to complete during their hospital in-patient visit. Participants will be asked to return the completed survey to their healthcare worker prior to leaving the hospital.

### **6.2 Work Package 2 (WP2): Patient/carer acceptability**

This qualitative WP2 will assess the key components that would make this feasibility trial and any future larger trial acceptable to patients. WP2 will be led by the VPLG Coordinator or suitable site staff delegate, with support from the Qualitative Researcher, CI and Trial Manager. This WP will focus on a discussion group looking at acceptability to patients and carers for use of the OLO (Sight Diagnostics) system to manage patients with chemotherapy-related suspected neutropenic sepsis and will be implemented prior to WP1.

**Figure 6.** Routine patient management pathway for patients presenting at pre-chemotherapy or paclociclib assessment with borderline neutropenia



Up to 15 members of the VPLG will be invited to participate in a discussion group meeting. Up to 10-15 patients and/or carers will take part. The interview will be held at the participating site, VCC or suitable alternative at the Cardiff. Participant consent will be collected remotely prior to the interview by the VPLG Coordinator or suitable site staff delegate. The interview will include a digital visual demonstration of the OLO System, including the testing equipment and blood sample collection consumables, implemented by the interviewer. The interviewer will use a list of key discussion topics to explore the views of the group about use of the OLO System to manage chemotherapy-related neutropenic sepsis. Key discussion topics will include but not be limited to:

- Views about the current patient management pathway (for example telephone triage, hospitalisation, administration of antibiotics prior to test results, etc.).
- Confidence in the OLO technology as an alternative to the standard test.
- Perceived benefits and disadvantages of the OLO technology.
- Views about the positioning of the OLO technology (for example, community, primary, secondary or tertiary care, Tenovus mobile unit).
- Views about the self-operation of a modified version of the OLO System or similar alternative device.
- Exclusion criteria for future large-scale study (if appropriate) based upon ability to use the equipment effectively, including dexterity and cognitive ability.
- Participant acceptance survey topics.

The discussion group meeting will be manually recorded in anonymised written note format and summarised in anonymised digital format (for example Microsoft Word). The summary will be used to assess the acceptability of the device and application to patients and their carers. It will also be used to develop a participant acceptability survey that, following approval by REC, will be used as a patient evaluation tool to assess acceptability of the equipment. This patient evaluation tool will be completed by participants of WP1, the device cohort comparator study, Cohorts 1-3.

This work will assist in the design of a larger trial and will involve liaison with:

- VPLG.
- Wales Cancer Research Centre (WCRC).
- Tenovus.
- Healthcare workers.

### **6.3 Work Package 3 (WP3): Healthcare worker acceptability**

This qualitative WP3 will assess the key components that would make this trial acceptable to healthcare workers. WP3 will be led by the Trial Manager, with support from a Qualitative Researcher. The WP will focus on a discussion group looking at acceptability to healthcare workers for use of the OLO System to manage patients with chemotherapy-related suspected neutropenic sepsis. The WP will be implemented as soon as possible during, or preferably, after the completion of WP1.

Staff at the WP1 participating site (VCC), Velindre University NHS Trust who are involved in the patient management, antibiotic treatment and sample testing pathway of patients with chemotherapy-related suspected neutropenic sepsis will be invited to participate in a discussion group interview. Up to 20 health care workers will be approached, with approximately 10-15 taking part. The interview will be held in remote digital format. Written informed consent will be collected remotely via email prior to the interview by the interviewee.

The interview will include a remote digital demonstration of the OLO System, including the testing equipment and blood sample collection device consumables delivered by the interviewer. The interviewer will use a list of key discussion topics to explore the views of the group about use of the OLO (Sight Diagnostics) system to manage chemotherapy-related neutropenic sepsis. Key discussion topics will include those detailed above plus:

- Ease of use of the OLO (Sight System (e.g. difficulties, device error rate, difficulties with implementation, and difficulties with interpreting instructions for use).
- Impact on timescales of patient management pathway.
- Preferable blood collection method (venous versus finger prick).
- Preferable location for the analyser within the hospital for different patient cohorts, e.g. laboratory vs clinic, in front or away from patient?
- Perceived benefits to patient and NHS.
- Other points of use in the patient management pathway, e.g. routine use at each regular pre-chemotherapy check during entire chemotherapy course for very susceptible patients?
- Lessons learned from the feasibility study that might impact on the design of a future larger study.
- Other non-cancer potential applications for the OLO System.

The discussion group meeting will be manually recorded in anonymised written note format and summarised in anonymised digital format (for example Microsoft Word). The summary will be used to assess the acceptability of the device and application to healthcare workers.

#### **6.4 Work Package 4 (WP4): Overall benefit to patients, feasibility of integration and economic impact.**

WP4 will assess the overall benefit to patients, feasibility of integration and economic impact of using the OLO System to manage patients with chemotherapy-related suspected neutropenic sepsis and will be implemented after the completion of WP1-3. The WP4 will be led by Planning and Performance Director and Innovations lead at Velindre University NHS Trust, with support from Velindre University NHS Trust management, industry (Sight Diagnostics), NHS Wales technology evaluation and Health economics (Swansea Centre for Health Economics, Swansea University) and the Welsh Government where applicable.

WP4 will identify the key areas relevant for implementation of the OLO System into clinical care, including evaluation within the context of a future larger national trial design. An options appraisal will be developed to optimise the strategy for taking a future larger trial forward. This will include economic, feasibility, and safety components with a view to a future funding bid. We will explore the framework required to adequately inform the potential integration of the investigational device and triage questions into routine practice, within Wales and beyond.

The group will use information from the above in collaboration with patient representatives to design a larger national UK trial suitable for funding via National Institute for Health Research (NIHR) Health Technology Assessment (HTA), the Medical Research Council or other third sector in collaboration with industry to formally assess the OLO System for routine use within the NHS. The aim is to assess cost effectiveness, including issues around hospital care/treatment and admissions. This will be achieved as a collaboration between patients, third sector, industry, clinical staff and the NHS and will involve liaison with:

- NHS Wales.
- Welsh Government.
- NICE.
- UKONS.
- The general public and other appropriate bodies.

## 6.5 Risk assessment

A trial risk assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm [16]. This risk assessment has been completed using a risk-adapted approach and includes:

- The known and potential risks and benefits to human subjects in relation to the device comparator study.
- All other risks related to the design and methods of the trial (including risks to participant safety, rights and wellbeing, as well as data integrity).
- How high the risk is, compared to standard practice.
- How the risk will be minimised/managed.
- COVID pandemic related risks and mitigations.

The ADVANCE trial intervention comprises an *in vitro diagnostic* (IVD) (OLO System) used in isolation following routine venous blood collection, or in conjunction with a finger prick lancet medical device (HTL-Strefa S.A. Prolance Max Flow Lancet (Lancet) or suitable locally or externally sourced routine alternative) to collect a new study finger prick blood sample. All devices are CE marked for use in the UK and will be used for the intended purpose of the respective CE mark. Therefore, the trial has been categorised as a low risk non-CTIMP study, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager as part of the local regulatory review process. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

## 7 Site and Investigator selection

This trial will be carried out at a single participating site (VCC) in Cardiff, Wales, UK. . A Principal Investigator will be assigned at site. The following documents must be in place and copies sent to the ADVANCE trial email account (see contact details on page 4) by the local VCC site team before the site can open to recruitment:

- Investigator Site File (ISF) initially supplied to site by the CTR.
- Favourable opinion of host care organisation/PI from REC.
- A signed delegation of duties document between the Sponsor/Site and CTR.

- Current Curriculum Vitae and GCP training certificate of the PI.
- Completed Site Staff Delegation Log [17] .
- Roles and Responsibilities document [18].
- A training log to evidence suitable training of staff delegated specific responsibilities on the Site Staff Delegation Log (for example, consent training for Senior House Officer (SHOs) responsible for recruiting and consenting participants to WP1).
- Full contact details for all host care organisation personnel involved, indicating preferred contact.
- A copy of the most recent approved version of the Participant Information Sheets and Consent Forms on host care organisation headed paper.
- A copy of the most recent approved GP letter on host care organisation headed paper.
- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses.
- Returned copy of the ADVANCE Self-Evident Correction Log [19] signed by the PI.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive the OLO System and consumables and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that the site obtains local R&D approval for the new documents.

Site initiation will be by attendance at a site initiation meeting, or by teleconference if attendance of key personnel is unfeasible.

## 8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before issue of relevant PIS/ ICF and registration and collection of consent.

### 8.1 Inclusion criteria

#### 8.1.1 WP1: Cohort comparator study

##### **Cohort 1: Suspected neutropenic sepsis**

- 1) 18 years old or over
- 2) Received cytotoxic chemotherapy or radiotherapy within the last 6 weeks and has signs and symptoms of neutropenic sepsis or infection and/or a temperature > 38°C or < 36°C
- 3) Admitted to any inpatient area at VCC for assessment for suspected neutropenic sepsis

##### **Cohort 2: Pre-SACT (Systemic anti-cancer therapy) ie borderline neutropenia or palbociclib**

- 1) 18 years old or over
- 2) Patients requiring up to date white cell differential or platelet count immediately prior to therapy i.e: Borderline neutropenia confirmed via a routine pre-chemotherapy whole blood neutrophil count, and require a repeat test either on the day of, or before, the next planned chemotherapy appointment or palbociclib therapy

##### **Cohort 3: Patients who have not had blood assessed by the OLO device but have received therapy that can cause a low white blood cell count.**

- 1) 18 years old or over
- 2) Patients receiving or who have received cytotoxic chemotherapy or radiotherapy

#### 8.1.2 WP2: Patient/Carer focus group interview

- 1) A member of the VPLG who is a current, or previous, cancer patient or carer of a cancer patient
- 2) 18 years old or over



### **8.1.3 WP3: Healthcare worker focus group interview**

- 1) 18 years old or over
- 2) Healthcare worker involved in the management pathway for neutropenic sepsis in cancer patients and/or medical device testing and/or implementation of new medical device at VCC and/or Velindre University NHS Trust

## **8.2 Exclusion criteria**

### **8.2.1 WP1: Cohort comparator study**

#### **Cohort 1: Suspected neutropenic sepsis**

- 1) Has leukaemia or CML.
- 2) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).

#### **Cohort 2: 'Borderline' neutropenia**

- 1) Has leukaemia or CML.
- 2) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).

N.B. Patients will not be excluded from either cohort if they are:

- Pregnant, lactating or breast feeding
- Have been vaccinated recently
- Have had neutropenic sepsis before

#### **Cohort 3: Survey only cohort**

- 1) Has leukaemia or CML.
- 1) Considered by their healthcare professional to be incapable of giving informed consent for any reason (for example senior review has identified severe sepsis).

### **8.2.2 WP2: Patient/Carer focus group interview**

- 1) Considered by VPLG Co-ordinator to be incapable of giving informed consent for any reason.

### **8.2.3 WP3: Healthcare worker focus group interview**

- 1) Considered by local PI to be incapable of giving informed consent for any reason.

## **9 Recruitment, Screening and registration**

### **9.1 Participant identification**

#### **9.1.1 WP1: Cohort comparator study**

We will approach and recruit a total of 90, 72 and 24 patients respectively to Cohorts 1, 2 and 3 as described in Section 14.1 Sample Size to take part in a non- randomised cohort medical device comparator feasibility study to clinically evaluate the safety and accuracy of using the OLO Sight System to manage chemotherapy-related suspected neutropenic sepsis.

The recruiting healthcare worker will screen the potential participant to ensure that they meet the WP1 eligibility criteria specified in Section 8.4 Inclusion criteria and 8.5 Exclusion criteria of the protocol, before obtaining the participant's consent. Participants will not be approach or registered into the study until the following routine assessments have been initiated for each cohort:

#### **Cohort 1:**

Following current UK NICE guidelines CG151 [3], UK cancer centres instruct patients on chemotherapy to take their temperature if they feel unwell, and to report this by telephone to the centre as soon as possible. These patients will be screened or triaged over the telephone using a set of standard triage questions following the UKONS Acute Oncology Initial Management Guidelines [20; see Appendix 1] and, if considered to have suspected sepsis will be admitted to hospital to undergo assessment. Such patients admitted to VCC will be managed following the local current procedure documented in Neutropenic sepsis: Prevention and Management of suspected and proven neutropenic sepsis at Velindre Cancer Centre [21].

All patients presenting with suspected neutropenic sepsis will have an urgent clinical assessment within 1 hour of admission, including the collection of standard blood samples from a vascular access device for standard peripheral blood cultures and laboratory tests, and administration of appropriate antibiotics.

Telephone triage and follow-up assessment data will be recorded locally at site using the Velindre UKONS Access spreadsheet following standard local procedure. The patient will normally remain in clinic as an inpatient for approximately 1- 4 hours before the standard laboratory tests will be available for initial consultant review.

Once the standard initial assessment process above has been completed, and whilst the patient remains in clinic awaiting their standard results, a member of the treating clinical team (SHO or nurse) who has been delegated the responsibility of recruitment and screening on the ADVANCE Site Staff Delegation Log will review the identifiable personal and clinical information held in the local hospital database(s) and hospital notes to assess if the patient meets the trial eligibility criteria (see Section 8 Participant selection) prior to consenting and registering the patient to the ADVANCE Cohort 1 following an electronic or backup manual registration procedure.

#### **Cohort 2: Pre-SACT requiring immediate white cell differential or platelet count i.e. 'Borderline' neutropenia or palbociclib**

Patients will attend clinic for a routine WBC count pre- treatment assessment prior to their planned new cycle of chemotherapy or palbociclib therapy to assess if they are well enough to receive treatment. If the test identifies 'borderline' neutropenia (via a borderline neutrophil (WBC) count) a repeat test will be arranged to be conducted before, or on the day of, the planned treatment. If the second test confirms 'borderline' or low neutrophils the patient's treatment may be postponed until the condition is resolved.

Patients identified as having an initial 'borderline' neutropenia test result, will be approached by a nurse (and/or appropriate delegate) within the normal treating clinical team who has been delegated the responsibility of recruitment and screening on the ADVANCE Site Staff Delegation Log. The nurse will review the identifiable personal and clinical information held in the local hospital database(s) and hospital notes to assess if the patient meets the trial eligibility criteria (see Section 8 Participant selection) prior to consenting and registering the patient to the ADVANCE Cohort 2. Where feasible, potential participants will be given a printed copy of the Cohort 2 PIS/ICF to read in clinic or in their own time outside of clinic. Alternatively, the patient's routinely collected email address may be used by the recruiting site staff for the sole purpose of issuing an electronic copy of the Cohort 2 PIS/ICF to eligible patients to facilitate reading at home and avoid retaining the patient in clinic longer than is

necessary to complete their routine care and/or comply with participating site COVID-incurred restrictions on local patient management pathways.

**Cohort 3: Patients who have not had blood assessed by the OLO device but have received therapy that can cause a low white blood cell count.**

Patients may be identified and invited to participate in the survey by members of the routine treatment team at Velindre Cancer Centre who have been informed of the ADVANCE study. Surveys will not request personal identifiable or special 'clinical' data, thus Cohort 3 participants will not be required to provide formal written consent and anonymous data will be collected under. The survey will include a brief written invite explaining that by completing and returning the survey the participant is providing implied consent. .

**9.1.2 WP2: Patient/Carer focus group interview**

Members of the general public who are registered with the Velindre Patient Liaison Group (VPLG) will be identified and screened by a VPLG Co-Ordinator. The VPLG Co-Ordinator will issue a copy of the WP2 PIS/ICF to up to 20 eligible members by hand at a VPLG meeting, or issued digitally via email to participants. This document includes an invite letter and reply slip. Members will be asked to return the reply slip either by hand or digitally by email to confirm if they would or would not like to take part, and their agreement to the VPLG Co-Ordinator to use their contact details already held on record for VPLG purposes to arrange an ADVANCE patient/carers group interview.

Patients/carers will not be recruited by publicity, i.e. posters, leaflets, adverts or websites.

**9.1.3 WP3: Healthcare worker focus group interview**

Healthcare workers at VCC, Velindre University NHS Trust in Wales, UK who are involved in the management pathway of patients with cancer-related suspected neutropenic sepsis will be identified by the local PI or suitable delegate within the local site team. The local PI or delegate will issue a copy of the WP3 PIS/ICF to up to 20 eligible members by hand or digitally via email. This document includes an invite letter and reply slip. The invitee will be asked to return the reply slip to the ADVANCE Trial Manager by email to [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) to confirm if they would or would not like to take part, and their agreement for the Trial Manager and/or Qualitative Researcher to use their work contact details to arrange an ADVANCE healthcare worker group interview. Healthcare Workers will not be recruited by publicity, i.e. posters, leaflets, adverts or websites.

## 9.2 Screening logs

### 9.2.1 WP1: Cohort comparator study

Delegated members of the local site team will manually enter all patients that are ineligible, eligible but not consented and/or approached/declined, including reasons, on a paper WP1 Cohort 1 and 2 Screening Log [22] so that any biases from differential recruitment will be detected. Personal identifiable information will be recorded at site on the log. An anonymised version of the log will be emailed to the CTR at [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) for review every 2-4 weeks during the recruitment phase (see section 19 for further detail on data monitoring/quality assurance). Cohort 3 eligibility, recruitment and data collection will be collated on an electronic screening log equivalent, e.g. Excel spreadsheet.

### **9.2.2 WP2: Patient/Carer focus group interview**

The VPLG Co-ordinator or suitable local site delegate will record all VPLG members that are ineligible, eligible but not consented and/or approached/declined on the paper WP2 Screening Log [23] and email the completed log to the CTR at [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) at the end of the recruitment phase. Personal identifiable information will be recorded. However, this will be re-dacted prior to submission.

### **9.2.3 WP3: Healthcare worker focus group interview**

The PI and or suitable delegate within the local site team will record all healthcare workers that are ineligible, eligible but not consented and/or approached/declined on the paper WP3 Screening Log [24] and will email the completed log to the [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) at the end of the focus group recruitment phase. Personal identifiable information will be recorded. However, this will be re-dacted prior to submission.

## **9.3 Recruitment rates**

### **9.3.1 WP1: Cohort comparator study**

60 patients will be approached and 48 participants recruited to Cohort 1: suspected neutropenic sepsis, and 30 patients will be approached and 24 participants recruited to Cohort 2: 'borderline' neutropenic sepsis; giving a total number of 90 patients approached and 72 participants recruited to the device comparator study at a single site over a recruitment period of approximately 3-6 months, i.e. an expected recruitment rate of approximately 12-24 participants per month in total. 24 patients will be approached to participate in Cohort 3: Survey only; with a view to obtaining a minimum of 19 completed and returned surveys.

### **9.3.2 WP2: Patient/Carer focus group interview**

Up to 20 patients/carers will be approached and 10-15 participants will be recruited to each of the patient and carer focus group interviews. Eligible members of the VPLG will be approached until enough have been recruited.

### 9.3.3 WP3: Healthcare worker focus group interview

Up to 20 healthcare workers will be approached and approximately 10-15 healthcare workers/participants will be recruited to the healthcare worker focus group interviews.

## 9.4 Informed consent

The participant's written informed consent must be obtained using the appropriate trial PIS/ICF [25-27] as follows:

**Table 1. WP1-3 PIS/ICF**

<b>WP1 Cohort 1</b>	ADVANCE WP1 Cohort 1 Device PIS/ICF
<b>WP1 Cohort 2</b>	ADVANCE WP1 Cohort 2 Device PIS/ICF
<b>WP2</b>	ADVANCE WP2 Patient Carer Discussion Group PIS/ICF
<b>WP3</b>	ADVANCE WP3 Healthcare Worker Discussion Group PIS/ICF

### 9.4.1 WP1: Cohort comparator study

With the exception of WP1 Cohort 3 participants, the patient's written informed consent must be obtained using the relevant ADVANCE WP1 Device PIS/ICF [25]. Patients should be given up to one hour after the initial invitation to decide if they wish to participate and to sign the ICF. This short decision period is essential to meet the required sample processing specifications of the OLO System, the number of hours in which the patient is likely to remain hospitalised or in clinic for their neutropenic sepsis.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the ADVANCE trial. Consent may be taken by a suitably GCP trained healthcare professional (e.g. Cohort 1, SHO or nurse; Cohort 2, nurse) who has been trained in recruitment and consent aspects of good clinical practice. Only when written informed consent has been obtained from the participant and they have been enrolled into the trial can they be considered a WP1 trial participant.

Participants should always be asked to sign an ICF. The ICF should be countersigned by the person taking consent. One copy should be given to the participant. The original copy should be kept in the local Investigator Site File (ISF). An additional copy should be kept with participant's hospital notes.

#### **9.4.2 WP2: Patient/Carer discussion group meeting**

The potential participant's written informed consent must be obtained using the ADVANCE WP2 Patient/Carer Discussion Group PIS/ICF [26]. The potential participant should be given sufficient time (at least 24 hours) after the initial invitation to participate before being asked to sign the Consent Form to decide if they wish to participate. The Participant should bring the blank ICF with them to the focus group meeting, or emailed to the organiser ahead of a virtual meeting. Informed consent must be obtained by the meeting leader using the ICF immediately prior to the participant taking part in the discussion group meeting, or verbally by the meeting leader prior to the start of a virtual meeting. Please note, only when written or verbal informed consent has been obtained from the participant can they be considered a WP2 patient/carer discussion group meeting participant.

Participants should always be asked to sign an ICF. The ICF should be countersigned by the person taking consent, or completed electronically if meetings are held virtually. One copy should be given to the participant. The original copy should be kept in the local Investigator Site File.

The right of the participant to refuse to participate in the group discussion meeting without giving reasons must be respected. The participant may withdraw consent to take part in WP2 at any time. They may leave the discussion at any time. They do not have to give a reason. They, and (if relevant) the person they care for, will still receive the same level of medical treatment as they would for standard care. If they decide not to take part their information will not be used in the study and their details will be removed from the study records. If they withdraw, they will be asked if they agree to the research team using their data. If they do not agree to their data being used then recorded data will be edited or deleted accordingly.

#### **9.4.3 WP3: Healthcare worker discussion group meeting**

The healthcare worker's written informed consent must be obtained using the ADVANCE Healthcare Focus Group PIS/ICF [27]. The potential participant should be given sufficient time (at least 24 hours) after the initial invitation to participate before being asked to sign the Consent Form. The Participant should bring the blank ICF with them to the focus group meeting or emailed to the organiser ahead of



a virtual meeting. Informed consent must be obtained by the meeting leader using the ICF prior to the participant taking part in the discussion group meeting, or verbally by the meeting leader prior to the start of a virtual meeting. Please note, only when written informed consent has been obtained from the participant can they be considered a WP3 healthcare worker discussion group meeting participant.

Participants should always be asked to sign an ICF. The ICF should be countersigned by the person taking consent, or completed electronically if meetings are held virtually. One copy should be given to the participant. The original copy should be kept in the local Investigator Site File.

The right of the participant to refuse to participate in the discussion without giving reasons must be respected. The participant may withdraw consent to take part in WP3 at any time. They may leave the meeting at any time. They do not have to give a reason. If they decide not to take part their information will not be used in the study and their details will be removed from the study records. If they withdraw, they will be asked if they agree to the research team using their data. If they do not agree to their data being used then the recorded data will be edited or deleted accordingly.

## **9.5 Registration**

WP1-3 participants will not be randomised.

WP1 Cohort 1 and 2 participants will be registered on the ADVANCE electronic trial database or a backup electronic registration list by a member of the local site team who has been delegated the responsibility of registration on the ADVANCE Site Staff Delegation Log. The database or back up list will require confirmation of the eligibility criteria before allocating a unique trial participant identification number to identify the participant.

The participants General Practitioner (GP) will be notified of the participants enrolment in ADVANCE using the ADVANCE GP Letter, if the participant gives consent to do so by initialling a separate box on the WP1 ICF.

WP1 Cohort 3 participants will be registered anonymously on an excel spreadsheet by the participating site.

WP2 and WP3 participants will be registered by the group discussion meeting leader on the WP2 and WP3 Screening Logs [23-24] respectively.

WP1-3 participants are permitted to be recruited to other clinical trials without prior discussion with the ADVANCE CI or the CTR.

## **10 Withdrawal & lost to follow-up**

### **10.1 Withdrawal**

Taking part in the ADVANCE trial is voluntary. The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis.

Similarly, the participant must remain free to withdraw at any time from part, or all, of the trial without giving reasons and without prejudicing his/her further treatment.

The ADVANCE Participant Withdrawal Form [28] will make it clear what part of the study the participant originally consented to take part in, and exactly what part of the study the participant is withdrawing from at either a single or multiple level as follows:

- Level 1: Withdrawal from WP1 Device comparator evaluation:
  - A: Withdrawal of permission to collect study sample(s) and their subsequent trial analysis.
  - B: Withdrawal from donation of previously collected study samples and their subsequent trial analysis.
  - C: Partial withdrawal from follow-up data collection specifying type of data (e.g. follow up).
  - D: Complete withdrawal from further data collection.
- Level 2: Withdrawal from WP2 Patient/Carer Discussion Group Meeting:
  - A: Withdrawal of data collected at the meeting.
  - B: Withdrawal from permission to use anonymised direct quotes obtained during the meeting in future publications or presentations.
- Level 3: Withdrawal from WP3 healthcare worker discussion group meeting
  - A: Withdrawal of data collected at the meeting.

- B: Withdrawal from permission to use anonymised direct quotes obtained during the meeting in future publications or presentations.

A participant may withdraw or be withdrawn from **WP1** Cohort 1 or 2 for the following reasons:

- Intolerance to interventional device (including SAEs and toxicities relating to the device and blood collection procedure)
- Non-compliance with the protocol
- Participant choice
- Clinician's decision (e.g. loss of capacity or safety issue)
- Incorrect registration (i.e. the participant does not meet the required inclusion/exclusion criteria)
- Other (as specified)

Withdrawal of consent is not applicable to participants taking part in WP1 Cohort 3 as these participants are not required to consent. The survey invite will explicitly state that once a survey has been submitted it, and the participants permission to use the anonymous data in it, cannot be withdrawn.

WP1 participants will not be withdrawn due to lost to follow-up.

A participant may withdraw or be withdrawn from **WP2 or WP3** for the following reasons:

- Non-compliance with the protocol
- Participant choice
- Interviewer (WP2) or PI (WP3) decision
- Incorrect registration (i.e. the participant does not meet the required inclusion/exclusion criteria)
- Other (as specified)

If a WP1-3 participant withdraws, any samples and/or research data collected before the date of withdrawal will be kept and analysed. No further data or samples will be collected from the participant for study purposes after the date they withdraw.

If a WP1 Cohort 1 or 2 participant withdraws, safety data ongoing at the time of withdrawal will continue to be collected, especially if the participant withdraws because of a safety event. For example, if a participant wishes to stop taking part in the trial completely, they may need to be seen one last time for an assessment.

If a WP2-3 participant withdraws they will be asked if they agree to the research team using their data. If they do not agree to their data being used, then recorded data will be edited or deleted accordingly.

In all instances participants who consent and subsequently withdraw consent should complete the ADVANCE Withdrawal Form supplied in the Site Initiation Pack. Alternatively, the withdrawal form should be completed on the participant's behalf by the researcher/healthcare professional based on information provided by the participant. This withdrawal form should be securely emailed to the CTR at [POCT@Cardiff.ac.uk](mailto:POCT@Cardiff.ac.uk).

Any queries relating to potential withdrawal of a participant should be forwarded by secure email to [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk).

## **10.2 Lost to follow up**

It is unlikely that WP1 Cohort 1 and 2 participants will be lost to follow-up due to a short follow-up period of 2-4 weeks and the requirement for the participant to regularly attend the clinic to receive standard non-trial follow up for suspected neutropenic sepsis and regular chemotherapy and other treatment for their cancer. Outcome data will still be collected from participants that do not fully adhere to the protocol, for example those that are lost to follow-up following their initial discharge from hospital. Lost to follow up is not applicable to WP1 Cohort 3, WP2 or WP3.

## **11 Trial Intervention**

### **11.1 WP1 Investigational Device - OLO (Sight Diagnostics) System**

The trial investigational device that will be assessed in WP1 is known as the OLO (OLO System). This system is a new and unique CE marked *in vitro* diagnostic point of care (POC) system for quantitative automated haematological analysis of whole blood. The system enumerates the following 19 CBC parameters inclusive of 5-part WBC differential: : WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, NEUT%/#, LYMPH %/#, MONO %/#, EOS%/#, and BASO%/#. The system uses image analysis software with Sight's proven and reliable technology, to provide accurate results within minutes.

. Sight have undertaken beta testing on patients with the Sight System and, whilst the results have not been scrutinised in a peer reviewed journal, it is clear that the results are considered accurate to give clinical guidance. However, we are keen to repeat such analysis in the initial stages of this feasibility study. No “real time” clinical decisions will be made based upon the results from the investigational device during this feasibility study. The participants and the NHS consultant(s) overseeing the management of the participant’s suspected neutropenic sepsis or borderline neutrophil count will not be told the results of the investigational device.

The OLO System comprises a scanning and analysing device and a CBC test kit which includes a disposable cartridge and sample preparation tool as shown in Figure 7. Sight OLO device and test kit.

Figure 7. Sight OLO System a) OLO-U1 Analyser, b) Test kit

a) OLO-U1 Analyzer



b) Test kit



The OLO-U1 (CBC Analyser) has the following specifications:

- Factory calibrated and requires no further calibration.
- Unique software is used for internal Quality Control (QC).
- Optional external QC verification using Sight QC Material stored at 2-8°C.
- Easy to use by non-laboratory personnel after a brief training.
- Sample preparation in under 1 minute from 2 drops of blood (utilised volume 27µl; required volume 30-700 µl dependent on sampling method)
- Measurement time of 10 minutes.
- Time from sample collection to result of 11-20 minutes.
- Throughput of 1 sample/11 minutes (scanning time can increase up to 15 minutes for abnormal samples), i.e. approximately 4 samples/hour.
- A small footprint.
- Weight 10kg
- Powered by wall power adapter.
- Operates at 0--60°C.
- Test kit storage 18-26°C.
- Test kit shelf life 13 months maximum.
- Barcode reading or manual entry of patient/sample ID
- Storage of up to 50,000 test results.
- Optional printing of results via remote or internet connected local printer
- Data transfer in single or multiple result format in .csv file format via USB or internet connection.
- 24 hour software updates and help desk support.

#### **11.1.4 ..... Blood sample restrictions collection**

Blood samples collected using the OLO K<sub>2</sub>EDTA venous blood tube or fingerprick sample preparation method should be tested using the OLO Analyser following the instructions provided in the OLO-U1 Analyzer Operating Manual [31].

The system is designed to establish agreement with the manual methods for the differential white blood cell count and total white blood cell count.

Bloods must be analysed using the OLO System as soon as possible, and within the timeframe specified in the Operating Manual.

#### **11.1.5 ..... Lancets**

Finger prick blood samples will be collected using a locally or externally sourced single-use Prolance Max Flow Lancet, blade 1.6mm (or suitable alternative) under the recommendation of Sight Diagnostics. Single use lancets must **not** be re-used, and must be safely disposed of according to local practice.

#### **11.1.6 ..... OLO System finger prick blood sampling**

Finger prick samples collected as described in Section 11.1.6 will be transferred to the OLO (Sight Diagnostics) disposable cartridge as described in the OLO-U1 Analyzer Operating manual

### **11.2 WP1 standard comparator system**

The standard whole blood analyser system used in the central Cardiff & Vale Laboratory at University Hospital Wales, Cardiff is the Yumizen 1500 and 2500, and at the satellite laboratory at VCC, Whitchurch, the Horiba Pentra DS120 or similar. These devices are automated high throughput systems capable of approximately 100 tests/hour using approximately 100-200µl sample volume and an autoloader. The systems test for multiple parameters including a 5-part WBC count and require an experienced operator. These systems will be used as the comparator system for evaluation of the OLO System in this trial and will be operated by the routine operator.

### **11.3 Investigational device operation**

Sight Diagnostics will supply two OLO-U1 analysers for the purpose of this trial which will be placed in a suitable location permitting access to the different operators for each WP1 Cohort: i) VCC acute admissions clinic Senior House Officers (SHOs) or nurses to evaluate blood samples donated from Cohort 1 Suspected neutropenic sepsis participants. ii) VCC Phlebotomists to test Cohort 2 'Borderline' neutropenia participant samples.

### **11.4 Compliance**

The OLO System analyser will display a flag or an Error Code if a problem is detected within the system or sample. The Operating Manual includes a trouble shooting guide which includes explanations and recommended actions for each flag or Error Code described. If the Troubleshooting Guide is unable to resolve a persistent problem, the site should contact either the Sight Diagnostic helpdesk using the details provided in the Operating Manual in the first instance, copying in the ADVANCE team at the CTR at [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) who will liaise with the Sight Diagnostics, to resolve the problem.

Some system flags and Error Codes require a replacement finger prick or venous blood sample aliquot to be taken. Consent for taking additional study samples under these circumstances for the purposes of WP1 will be included in the relevant WP1 Participant PIS/ICF.

The ADVANCE database will include fields to permit the collection and analysis of device flags, Error Codes, and sample re-takes.

The CTR will review the ADVANCE database to assess compliance to the WP1 investigational device operating procedures and protocol approximately halfway through the predicted device assessment phase.

Any non-compliances to the WP1 sections of the Protocol identified at site will be reported by the site to the CTR immediately and followed up by the CTR following the CTR GCP/Protocol Non-Compliances and Serious Breaches SOP Where appropriate, a triggered site visit may be conducted by the CTR.



## 12 Trial procedures

### 12.1 WP1: Cohort comparator study

#### 12.1.1 ..... WP1 screening assessments

On average we anticipate participants will participate in WP1 for a period of up to one month from the date of registration to the end of trial follow up. There will be no cost to the participant for participating in the trial. Participants will not be paid for participating in the trial. The participant will not be required to have any additional medical checks or medication, or attend the hospital more frequently, during the course of the study than they would if they do not participate.

The Participant must not be given the relevant WP1 PIS/ICF until after the routine non-trial assessments, treatment and sample collections for the relevant cohort have been completed as specified in Section 9.

After taking written informed consent, but before registering a patient in the study, the patient's healthcare professional will collect some screening information to confirm they are eligible to take part in the study (See Section 9.4).

#### 12.1.2 ..... WP1 trial-specific blood sample collection

Following registration, the following study blood samples will be collected from each participant for testing using the investigational device from participants recruited to Cohort 1 or 2:

1x 30µl new study sample of whole blood collected using the finger prick method and a Prolance Max Flow Lancet (or suitable locally or externally sourced alternative) and transferred to a OLO (disposable cartridge using the method described in the OLO System Operating Manual (i.e. 1 replicates).

OR

1x 700µl new study sample aliquot taken from a previously collected routine K<sub>2</sub>EDTA venous blood tube sample using the blood tube dispensers provided.

A second study sample (new fingerprick or existing venous sample aliquot) will be collected if the original study sample results in a test result error.

Study samples will be tested using the OLO (Analyser following the instructions provided in the OLO- Operating Manual [31], before the participant is discharged from hospital. The test result will be obtained <10 minutes after inserting the microcuvette into the analyser.

Consent and sample collection must be initiated as soon as possible after completion of the standard non-trial assessments, treatment and sample collections.

Study samples must not be removed from routine venous samples until the sample has stood for **at least 20 minutes**. If this process will prevent the routine sample from reaching the routine laboratory within the required local and/or national permitted timeframe a finger prick sample must be taken instead.

Samples tested in the OLO (Sight Diagnostics) analyser will be destroyed following local hospital procedures immediately following conduct of the study test. The samples will not be stored for future research.

The participant and their treating hospital consultant will only be told the results from their standard care tests. The result from the study tests will **not** be used to manage the participant.

If the standard care test(s) show that the participant has neutropenic sepsis their treating hospital consultant will decide what treatment they need (for example whether or not they need to continue taking antibiotics, stay in hospital, or can be discharged) in discussion with the participant and following local standard procedure.

### **12.1.3 .....ADVANCE Qualitative Acceptability Survey**

Prior to discharge from the hospital, Cohort 3 participants will be given a paper copy of the ADVANCE Survey [33] to complete about their views around the study and our intended use of the new equipment

The healthcare professional will ask the patient to complete the survey before they leave the hospital following their discharge. The survey will take about 30 minutes for the participant to complete. Completed surveys will be handed to the local PI.

**12.1.4 ..... Baseline toxicity data**

Baseline toxicity data will be collected after consent and prior to collection and analysis of study blood samples. SAEs must be reported following the timeframes and procedures specified in Section 13.

**Table 2. Schedule of enrolment, device and comparator interventions and assessments for WP1 <sup>1</sup>**

	Non-Trial Assessments	Informed Consent	Screening Assessment	Trial registration	Assessment 1 Baseline	Assessment 2 Follow Up
<b>Days</b>	0	0	0	0	0	14-28
<b>Hours</b>	0-5	0-5	0-5	0-5	0-5	N/A
<b>All Cohorts</b>						
Given relevant WP1 PIS/ICF <sup>5</sup>	X					
Informed consent <sup>6</sup>		X				
Eligibility assessment (including review of medical history and triage data for relevant cohorts)			X			
Trial registration				X		
Withdrawal as applicable					X	X
<b>Cohort 1 Only</b>						
Routine telephone triage	X					
Routine hospital admission for suspected neutropenic sepsis, inclusive of routine non-trial assessment, antibiotic treatment and venous blood sample collection	X					
<b>Cohort 2 Only</b>						
Routine attendance at phlebotomy for routine pre-chemotherapy or paclociclib assessment, including repeat white blood cell count due to prior 'borderline' neutropenia test result	X					
<b>Cohort 1 and 2 Only</b>						
Baseline toxicity assessment					X	
Collect finger prick or venous K <sub>2</sub> EDTA study blood sample and analyse using OLO System <sup>2</sup>					X	
SAE safety assessment <sup>3</sup>					X	X
Enter standard test, antibiotic treatment, hospital discharge and follow up data on ADVANCE database					X	
Collection of follow up data as applicable						X
<b>Cohort 3 Only</b>						
Given WP1 Cohort 3 Anonymous Acceptability Survey					X	
Complete and return Acceptability Survey prior to discharge <sup>4</sup>						X

<sup>1</sup> Taken from the HRA CTIMP protocol template (2016).

<sup>2</sup> Must be taken and analysed before the participant is discharged from hospital.

<sup>3</sup> Baseline toxicity data to be collected after consent and prior to collection and analysis of study blood samples. SAEs must be reported following the timeframes and procedures specified in Section 13.

<sup>4</sup> Participants should be reminded to return their survey prior to leaving the hospital following discharge..

<sup>5</sup> Participant must not be given the relevant WP1 PIS/ICF until after the standard non-trial assessments, treatment and sample collections have been completed.

<sup>6</sup> Consent to be taken after completion of routine neutropenic sepsis assessments and starting antibiotics for Cohort 1 participants.

### **12.1.5 ..... Baseline and follow up assessments**

During participation in the study we will collect information about the patients suspected neutropenic sepsis, antibiotic treatment, hospital discharge, and follow up from their medical records and other data systems (for example, CANISC, Chemocare, local UKONS ACCESS-based spreadsheet) held within Velindre University NHS Trust.

If the patient develops a new medical condition, or an existing condition worsens during participation in the study or at a withdrawal visit, then the healthcare professional may contact the patient and ask them about this, until it has completely resolved.

### **12.1.6 ..... Investigation device test results**

The results of the investigational device blood tests will not be shared with the participant or used to manage the treatment pathway of the patient. The treating consultant will be told the results of the study tests after the participants condition has been successfully treated so that we can find out if it would have changed how the participant was treated. We intend to use the results of this feasibility study to inform the development of a larger UK-wide randomised study in which we intend to use the results of the investigational device(s) to manage patient pathways.

### **12.1.7 ..... Review of existing neutropenic sepsis data held at site**

The VCC Service Improvement team conducts regular audits of UKONS neutropenic sepsis data to meet UK UKONS reporting requirements. The team will provide existing clinical data routinely collected from the type of patient eligible for WP1 Cohorts 1 and 2 to the CTR for analysis and review in parallel to the WP1 device cohort study data. Fully anonymised audit data will be transferred to the CTR following CTR and Sponsor data protection guidance and procedures, and analysed alongside the other WP1 and WP2-3 data by the Statistician.

## **12.2 WP2: Patient/carer discussion group meeting**

Up to 20 members of the VPLG will be invited to participate in WP2 and given a copy of the ADVANCE WP2 PIS/ICF [26] by the recruiting VPLG Co-ordinator as specified in Section 9. The member will be

asked to return the reply slip on page 2 of the document by email or post to the VPLG Co-ordinator. Members who decline to take part must not be contacted further by the recruiting VPLG Co Ordinator for the purposes of the trial. The recruiting VPLG Coordinator will liaise with the VPLG member and the ADVANCE Trial Manager to arrange attendance at a discussion group meeting to be held at VCC in Cardiff, UK or a suitable alternative location at the University of Wales Hospital, Heath Site or Cardiff University, at a specified future date and time, or using a virtual video conferencing platform if required.

**Table 3. Schedule of invitation, consent and implementation of WP2 patient/carer discussion group meeting<sup>2</sup>**

	Pre-Consent	Informed Consent	Post-Consent
<b>Weeks</b>	0	8 <sup>5</sup>	8
VPLG member given WP2 PIS/ICF (including invitation letter) by recruiter (VPLG Coordinator or suitable site delegate) at a routine VPLG meeting	X		
Participant completes and returns reply slip confirming if they agree to be contacted about attending a discussion group meeting <sup>2</sup>	X		
Recruiter liaises with member and ADVANCE Trial Manager to arrange attendance at discussion group meeting	X		
VPLG Co-Ordinator takes Informed consent prior to discussion <sup>3</sup>		X	
Discussion group meeting (duration approximately 1.5 hours)			X
Withdrawal as applicable <sup>4</sup>			X

<sup>1</sup> Taken from the HRA CTIMP protocol template (2016).

<sup>2</sup> Participants that decline to take part must not be contacted further for the purposes of this trial.

<sup>3</sup> Participant must be given a minimum of 24 hours after receipt of the PIS/ICF before informed consent is taken.

<sup>4</sup> Participant, or researcher/clinician must complete a copy of the ADVANCE Withdrawal of Consent Form and email to [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) immediately.

<sup>5</sup> The discussion group meeting will be conducted as soon as possible after the VPLG member has agreed to further contact about the meeting, and where feasible within 8 weeks.

### 12.3 WP3: Healthcare worker discussion group meeting

Approximately 15 healthcare workers will be invited to participate in WP3 and given a copy of the ADVANCE WP3 PIS/ICF [27] by a member of the local site trial team assigned the role of recruiting participants on the local site staff delegation log as specified in Section 9. The potential participant will be asked to return the reply slip to the recruiter by email or hand. Potential participants who decline to take part must not be contacted further by the recruiter for the purposes of recruitment. The local trial team will liaise with the potential participant and the ADVANCE Trial Manager to arrange attendance at a discussion group meeting to be held at VCC or a suitable alternative location

at the University of Wales Hospital Heath Site or Cardiff University at a specified future date and time, or using a virtual video conferencing platform if required.

**Table 4. Schedule of invitation, consent and implementation of WP3 healthcare worker discussion group interview<sup>3</sup>**

	Pre-Consent	Informed Consent	Post-Consent
<b>Weeks</b>	0	8 <sup>5</sup>	8
Healthcare worker given WP3 PIS/ICF (including invitation letter) by recruiter	X		
Healthcare worker completes and returns reply slip confirming if they agree to be contacted about the focus group meeting <sup>2</sup>	X		
Recruiter liaises with member and ADVANCE Trial Manager to arrange attendance at discussion group meeting	X		
Trial Manager takes Informed consent prior to discussion <sup>3</sup>		X	
Discussion group meeting (duration approximately 1.5 hours)			X
Withdrawal as applicable <sup>4</sup>			X

<sup>1</sup> Taken from the HRA CTIMP protocol template (2016).

<sup>2</sup> Participants that decline to take part must not be contacted further for the purposes of this trial.

<sup>3</sup> Participant must be given a minimum of 24 hours after receipt of the PIS/ICF before informed consent is taken.

<sup>4</sup> Participant or Trial Manager must complete a copy of the ADVANCE Withdrawal of Consent Form and email to [POCT@cardiff.ac.uk](mailto:POCT@cardiff.ac.uk) immediately.

<sup>5</sup> The discussion group meeting will be conducted as soon as possible after the healthcare worker has agreed to further contact about the meeting, and where feasible within 8 weeks.

## 12.4 Implementation of the WP2 Patient/Carer and WP3 Healthcare worker discussion group meetings

The potential participant will be asked to bring the relevant WP2 or WP3 PIS/ICF [26, 27] with them to the meeting, and to sign the ICF upon on arrival at the meeting before the discussion starts or emailed to the organiser ahead a virtual meeting and verbally consented prior to the start of a virtual meeting, as specified in Section 9. The meeting will last about 60-90 minutes and will be arranged at a date and time convenient to those taking part. The interview will be held at VCC in Cardiff where feasible, or at either the University Hospital of Wales, Heath Park Site or Cardiff University campus, or using a virtual video conferencing platform if required. About 10-15 participants will take part in each meeting.

The WP2 patient/carers meeting will be led by one or more VPLG Coordinator(s) who is employed at the participating site and has experience of discussing cancer research with patients and their carers in the group setting.



The WP3 healthcare worker meeting will be led by a member of the CTR ADVANCE team with a background in cancer and/or qualitative research.

Representative(s) from the ADVANCE trial team will be present as observers. The total number of people present at each meeting will be no more than 20.

After consent and prior to the discussion, the OLO System will be digitally demonstrated to explain how it can be used to detect a low white blood cell count. The meeting leader will then ask the participants their views about potential use of the system to manage cancer patients who have suspected neutropenic sepsis whilst receiving chemotherapy following a list of question topics that has been approved by REC. The interviewer and/or observers will make handwritten notes to record the discussion. The participants will be able to ask the leader to pause the meeting at any time. At the end of the meeting, the leader will check once again that each participant continues to provide consent for their conversation to be included in the trial.

WP2 participants who are cancer patients will be permitted to leave the interview early if they are thought to be fatigued or become unwell.

WP2 and WP3 participants will not be paid for participating in this study and the study may not benefit them personally. Participants will have to arrange their own transport to the meeting, if applicable, and will not be paid travel expenses.

## **12.5 Development of WP1 Participant Acceptability Survey**

The WP1 device evaluation will take place after WP2. The patient/carer discussion group meeting will be used to inform the design of a survey to record the experience of cancer patients recruited to WP1 Cohort 3.

## **13 Safety reporting for WP1 Cohorts 1 and 2**

All safety aspects of the trial will be documented in the ADVANCE Safety Management Plan [34].

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

The investigational IVD (OLO (System) is non-invasive and OLO (System) results will not be used to manage participants. Therefore, there is no risk of adverse events associated with the OLO System and reporting of such events is not required.

The investigational medical device (Lancet) used to collect trial-specific finger prick blood samples is invasive and there is a low risk that WP1 participants may experience an Adverse Event (AE). Therefore, Serious Adverse Event (SAE) reporting is required.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and safety specialist unless the SAE is specified as not requiring immediate reporting (see section 13.2).

### 13.1 Definitions

**Table 5.** SAE terminology definitions

<b>Term</b>	<b>Definition</b>
<b>Adverse Event (AE)</b>	Any untoward medical occurrence in a participant or clinical trial participant administered a medical device and which are not necessarily caused by or related to that product
<b>Serious Adverse Event (SAE)</b>	Any adverse event (SAE) that - <ul style="list-style-type: none"> <li>• Results in death</li> <li>• Is life-threatening*</li> <li>• Required hospitalisation or prolongation of existing hospitalisation**</li> <li>• Results in persistent or significant disability or incapacity</li> <li>• Consists of a congenital anomaly or birth defect</li> <li>• Other medically important condition***</li> </ul>
<b>Unexpected Serious Adverse Effect (USAE)</b>	A serious adverse event (SAE) which by its nature, incidence, severity or outcome has not been identified in the protocol or risk assessment and is previously undocumented.

**\*Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**\*\* Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

**\*\*\* Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

## 13.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements above, for the purposes of this trial the following events will be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Puncture wound, infection, inflammation, or swelling at the site of the lancet finger prick  
Grade ≤2

For the purposes of this trial the following events will **not** require reporting:

- Hospitalisation for neutropenic sepsis
- Death due to neutropenic sepsis
- Any abnormal laboratory measurement associated with the routine or investigational test used to diagnose neutropenic sepsis

**These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.**

## 13.3 Causality

Causal relationship will be assessed for the intervention:

<b>Device intervention:</b> HTL-Strefa S.A. Prolance Max Flow Lancet or similar
---------------------------------------------------------------------------------

The Principal Investigator (or another delegated medically qualified doctor from the trial team) will assess each SAE to determine the causal relationship and the CI (or another appropriately qualified member of the TMG) can also provide this assessment where necessary:

<b>Relationship</b>	<b>Description</b>	<b>Reasonable possibility that the SAE may have been caused by the intervention?</b>
<b>Unrelated</b>	There is no evidence of any causal relationship with the intervention	No
<b>Unlikely</b>	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
<b>Possible</b>	There is some evidence to suggest a causal relationship with the intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
<b>Probable</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
<b>Definite</b>	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

#### **13.4 Expectedness**

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

SAEs which add significant information on specificity or severity of a known, already documented ADE constitute unexpected events, i.e. an unexpected serious adverse device event (USAE). For example, an event more specific or more severe than that described in the protocol is considered unexpected.

**Table 5.** Table of expected events for the intervention

<b>Event</b>
Puncture wound, infection, inflammation, or swelling at the site of the (study finger prick Grade $\geq 2$

### **13.5 Reporting procedures**

#### **13.5.1 ..... Participating Site Responsibilities**

The PI (or delegated appropriately qualified doctor from the trial team) should complete a copy of the ADVANCE SAE Case Report Form (CRF) [35] and sign and date the CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

The completed CRF for all events requiring immediate reporting should be submitted via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by ADVANCE Participant Trial Number and age at time of SAE. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

**Serious Adverse Event (SAE) email address:**  
[CTR-Safety@Cardiff.ac.uk](mailto:CTR-Safety@Cardiff.ac.uk)  
**SAE Fax number:**  
**0203 0432 376**  
**(for emergency use only when email is not available)**

SAEs should be reported from time of signature of the WP1 ICF, throughout the follow-up period up to, and including 28 days after the date upon which the WP1 lancet was used on the participant.

A SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- A SAE
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted, and the information must be provided by the site to the CTR within 24 hours.

All other ADEs should be reported on the CRF following the CRF procedure described in Section 16.

**13.5.2 ..... The CTR responsibilities**

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs to the REC until 28 days after the participant receives the last part of the intervention, (i.e. from date of finger prick).

Once a SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

For all non-CTIMP studies, including clinical investigations of medical devices, only reports of related and unexpected Serious Adverse Events (SAEs) should be submitted to the REC. These should be sent within 15 days of the chief investigator becoming aware of the event.

There is no requirement for annual safety reports to REC in addition to the information provided through the annual progress report.

### **13.6 IVD and medical device defect and deficiency reporting**

Sites will be responsible for reporting suspected problems or incidents with the CE marked investigational devices (e.g. OLO (System and components, or Lancet) directly to the MHRA via the MHRA Yellow Card Scheme following local and MHRA procedures.

The device manufacturers (OLO (and lancet manufacturer) will be responsible for reporting defects and deficiencies of the devices directly to the MHRA via the MHRA Manufacturer’s On-line Reporting Environment (MORE) national reporting system following manufacturer and MHRA procedures.

### **13.7 Contraception and pregnancy**

#### **13.7.1 ..... Contraception**

There is no requirement for women of childbearing potential entering into this trial, or male participants with such a partner to use a contraceptive during of following participation in the trial.

#### **13.7.2 ..... Pregnancy reporting whilst participating in the trial**

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, or a congenital anomaly or birth defect associated with the intervention device, is highly unlikely and not considered an SAE. Therefore, this trial will not require pregnancy reporting or follow-up.

### **13.8 Urgent Safety Measures (USMs)**

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the REC immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR USM reporting processes.

## **14 Statistical considerations**

### **14.1 Sample size**

#### **14.1.1 WP1 Device cohort study**

##### **Cohorts 1 and 2 combined:**

We will evaluate the concordance between the OLO neutrophil result and the standard of care laboratory result from the same time period, across all patients with a valid output. A valid OLO neutrophil result will be one which produces a test result which is within  $\pm 0.2 \times 10^9/L$  of the standard laboratory result.

##### **Cohort 1 Suspected neutropenic sepsis:**

60 patients will be approached over a three-month period to participate in Cohort 1. If 80% of those approached are recruited (are eligible and provide consent), 48 patients will provide a 95% confidence interval of 68.2% to 88.2%. The widest the 95% confidence interval would be, with an estimated proportion of 50%, 37.7% to 62.3%.

If a valid OLO neutrophil test result is obtained from 90% of recruited patients, 43 patients will provide a 95% confidence interval of 77.8% to 95.5%. If a survey is completed and returned by 80% of recruited patients, 38 patients will provide a 95% confidence interval of 65.7% to 88.3%. In both instances, the widest the 95% confidence interval would be, with an estimated proportion of 50%, 36.4% to 63.6%.

##### **Cohort 2 Borderline neutropenia/pre SACT evaluation:**

30 patients will be approached over a three-month period to participate in Cohort 2. If 80% of those approached are recruited (are eligible and provide consent), 24 patients will provide a 95% confidence interval of 62.7% to 90.5%. The widest the 95% confidence interval would be, with an estimated proportion of 50%, 33.2% to 66.9%.

If a valid investigational device test result is obtained from 90% of recruited patients, 22 patients will provide a 95% confidence interval of 74.2% to 97.7%.

##### **Cohort 3 Survey Only**



24 patients will be approached over a one-three month period to participate in WP1 Cohort 3. If 80% of those approached are recruited (are eligible and return an anonymous survey), 19 patients will provide a 95% confidence interval of 59.5% to 90.8%.

In all instances, the widest the 95% confidence interval would be, with an estimated proportion of 50%, 31.4% to 68.6%.

#### **14.1.2 WP2 and WP3 discussion group meetings**

Approach 20 patients/carers (WP2) or healthcare workers (WP3). Recruit 10-15 participants max to each group. Detailed statistical analysis will not be conducted for WP2 and WP3 due to the qualitative nature of the research. Further details of qualitative analysis of discussion group recruitment and attendance data is provided in Section 15.1.

## **14.2 Missing, unused & spurious data**

The OLO ( System Operating Manual describes the expected white blood cell values for normal adults

The values may vary due to a wide range of factors, such as sex, diurnal variations, exercise, physical stress or trauma, pregnancy, indigestion of food, and cigarette smoking. The OLO-U1 Analyzer automatically assesses the OLO result against one of two pre-defined ranges (female age 22 years+ or male age 22 years+) and flags values outside of these normal values.

When capillary skin puncture is performed, several defence systems in the body are activated very quickly. These defence systems cause an increase in the number of WBCs in the blood closest to the wound, leading to greater differences in results from several samples taken from the same finger stick.

The participating sites normal laboratory ranges for a white blood cell and differential blood count will be sent to the CTR during site set up and will be taken into account when analysing the trial data.

For the purpose of ADVANCE the OLO-U1 Analyser will be programmed to compare the results against these standard local lab ranges for adult males and females.

A detailed Statistical Analysis Plan (SAP) [36] will be in place prior to the main trial database lock and analysis.

### **14.3 Procedures for reporting deviation(s) from the original SAP**

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

### **14.4 Termination of the trial**

There will be no formal stopping rules or discontinuation criteria based on the low risk non-CTIMP trial design, however the TMG will assess SAE data at TMG meetings during the recruitment and follow up phase and escalate if deemed appropriate.

### **14.5 Inclusion in analysis**

Data derived from all participants in WP1-3 will be included in the analysis unless consent to do so has been specifically withdrawn on the ADVANCE Withdrawal CRF [28].

## **15 Analysis**

### **15.1 Quantitative analysis of WP1 device cohort evaluation**

All quantitative analysis will be documented in the SAP [36] prior to implementation of the analysis.

As this is a feasibility study, statistical analysis of study outcomes will be descriptive in nature. Continuous data will be reported as means and standard deviations, or medians and interquartile ranges, as appropriate. Categorical data will be reported as frequencies and proportions. Outcomes will be estimated with their associated 95% confidence intervals.

No formal hypothesis testing will take place.

While subsequent funding is not formally linked to satisfying any specific progression criteria, we propose the following as indicators that a larger study is feasible (NB. Failure to meet one or more of the criteria would indicate that modifications are required, with potentially further feasibility testing, prior to a larger study) as described in Table 7.

**Table 7.** Trial progression criteria

<b>Outcome</b>	<b>Criteria</b>
Recruitment	At least 80% of patients approached to take part provide consent
Intervention adherence	At least 90% of recruited participants receive the OLO test
Intervention fidelity	A valid test result is obtained from at least 90% of recruited participants who receive the OLO test
Survey fidelity	A survey is completed and returned from at least 80% of recruited participants who are given the survey
Data collection	At least 80% of recruited participants have clinical outcome data available for statistical analysis
Staff focus groups	Focus group data indicates that the OLO test is acceptable
Patient focus groups	Focus group data indicates that the OLO test is acceptable

There will be no interim analyses other than TMG review of WP1 SAE's at TMG meetings, Trial Manager review of screening logs through the WP1-3 recruitment phases, and Trial Manager review of data entry after approximately half of the participants have been recruited to WP1.

### **15.2 Qualitative analysis of WP1 Patient Acceptability Survey**

All qualitative analysis will be documented in the Qualitative Analysis Plan (QAP) [37] prior to implementation of the analysis.

### **15.3 Qualitative analysis of WP2 and WP3 discussion group meeting data**

The qualitative component of this trial aims to assess the acceptability of the System for the purpose of management of chemotherapy-related neutropenic sepsis to patients, carers and healthcare workers. Anonymised handwritten notes, taken at the meeting by the meeting leaders and/or observers, will be transcribed by meeting leader into electronic digital format (for example Microsoft Word). Data will be summarised to identify problems with the OLO (System and trial procedures that need addressing as well as patient, carers and healthcare workers attitudes and experiences. A more detailed framework analysis will not be conducted due to the feasibility nature of the study and limited funds. Anonymised data will be represented by selected extracts. The results will be discussed with data extracts used in support of claims made. The TMG will analyse the results to assess potential alterations to the trial design to inform the development of a larger UK-wide funding application, to include an amended survey and full framework analysis, and to complement the reporting of the full trial.

Potential publications resulting from the qualitative study will not be reported before the completion of the main trial if any aspect of this will cause a negative affect or compromise the trial in any way. The decision to publish results arising from the qualitative elements of the study before the end of the main trial, or not, will be made by the TMG and Executive Group.

#### **15.4 Cost effectiveness analysis**

In WP4 the TMG will analyse health utility and economic data (for example bed usage, antibiotic treatment and blood test costs) collected in WP1 via various routine UKONS data collection, a local audit of UKONS data run in parallel to the WP1 device cohort study, and WP1 patient surveys, to identify key cost drivers. The results will be used to inform the design of a future larger UK-wide trial, including anticipated effect sizes for the larger trial, which will include a cost utility study.

## **16 Data Management**

### **16.1 Data collection**

Data collection procedures will be documented in the Data Management Plan (DMP) [38].

Source Data is defined as *“All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.”* There is only one set of source data at any time for any data element.

The ADVANCE trial will collect several different types of source data from a variety of sources as defined in Tables 8 and 9 below:

**Table 8.** ADVANCE WP 1 Source Data

	Medical records/ local UKONS data	Miscellaneous NHS database	Laboratory database	Pharmacy records (e.g. CANISC Chemocare)	MASCC Risk Assessment	OLO System (device)	ADVANCE database	ADVANCE WP1 paper/CF	ADVANCE Paper WP1 Withdrawal CRF	SAE Electronic CRF	ADVANCE WP1 screening log	Participant Surveys
<b>Cohort 1</b>												
Pre- hospital admission triage	X	X										
Hospital admission	X	X										
Standard laboratory tests including FBC, U+Es, LFTS, CRP, microbiology culture	X	X	X									
Antibiotic prescribing	X	X		X								
Care escalation (e.g. critical care)	X	X										
Senior clinical review including MASCC risk assessment	X	X			X							
<b>Cohort 2</b>												
<u>Borderline neutropenic sepsis data</u>	X	X										
<u>Chemotherapy repeat assessment data</u>	X	X										
<b>Cohorts 1 and 2</b>												
Trial screening / eligibility	X	X									X	
Trial consent							X				X	
Trial registration							X				X	
Baseline date (prior sepsis, toxicities)	X	X	X	X								
OLO System study blood sample and tests						X	X					
Hospital discharge	X	X										
Standard local follow-up	X	X										
Trial follow-up							X					
Trial adverse events										X		
Trial withdrawal								X				
<b>Cohort 3</b>												
Participant acceptability												X

**Table 9.** ADVANCE WP2 and 3 Source Data

	NHS database	VPLG database/records	ADVANCE database	ADVANCE paper ICF and/or reply slip	ADVANCE WP2 Paper Withdrawal CRF	ADVANCE WP3 Paper Withdrawal CRF	ADVANCE & WP2 screening log	ADVANCE & WP3 screening log	Leader/observer notes recording	Digital summary or notes
<b>WP2 Patient/Carer Focus Group</b>										
<i>Trial screening/eligibility</i>		X					X			
<i>Trial consent</i>				X						
<i>Patient/carer acceptability</i>									X	X
<i>Trial withdrawal</i>					X					
<b>WP3 Focus Groups</b>										
<i>Screening/eligibility</i>	X							X		
<i>WP2/WP3 consent</i>				X						
<i>Healthcare worker acceptability</i>									X	X
<i>Trial withdrawal</i>						X				

## **16.2 Completion of CRFs**

It is intended to develop a web-based ADVANCE database that the sites team will use to record all data collected in WP1. The database will be a secure encrypted system accessed by an institutional password, and will comply with the General Data Protection Regulation 2018. The system will be accessed at a link provided during site set up.

A user password will be supplied to the local PI and/or suitable delegate named on the site delegation log as being responsible for data entry upon completion of the green light WP1 site activation procedure.

The database will include a variety of web-based data collection forms including registration, baseline, treatment and follow up, and routine and study blood test samples and results.

Paper CRFs will be developed as an emergency backup to web-based remote database entry, e.g. server inaccessible. When in use paper CRFs will be completed by site staff and securely emailed to the CTR at [ADVANCE@cardiff.ac.uk](mailto:ADVANCE@cardiff.ac.uk). Upon receipt at the CTR, paper CRFs will be entered by the CTR Data Manager onto the web-based database as soon as feasible. QC checks of non-entered paper CRFs will be conducted on a regular basis by the CTR Data Manager as specified in the ADVANCE Trial Monitoring Plan (40).

Detailed plans for data entry and coding, including any processes to promote data quality (e.g. double data entry etc) will be detailed in the ADVANCE Data Management Plan, which will be drafted prior to the collection of any trial data following CTR Data Management Policy and SOP.

The participating site will be trained in what, when and who can enter data for each WP1 patient cohort prior to site activation to recruitment.

## **16.2 WP2 and WP3 qualitative data management**

All qualitative discussion group meetings will be manually recorded in anonymised hand-written note format to record any instances of non-verbal communication or reactions to any of the discussions. The notes will be summarised anonymised digital format (for example Microsoft word) and uploaded onto a secure computer at the CTR, stored on a secure server and labelled with a unique identifier. Participants will be asked to consent to the use of their anonymised extracts of talk in the study report and future publications.

## **17 Protocol/GCP non-compliance**

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

## **18 End of Trial definition**

The WP1 Cohort Comparator study phase will be followed by a non-interventional follow-up period which will continue to observe participants until resolution of their neutropenic sepsis. All participants will be followed up for SAEs until 28 days after the date of collection of the study blood samples.

For the purpose of REC approval, the study end date is deemed to be the date of last data capture to meet the trial endpoints. This will be the date upon which all WP1 data has been entered on to the trial database, all WP2 and WP3 data has been collected, and all surveys have been collected. The Sponsor must notify the main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

## **19 Archiving**

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years from the date of last data capture. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site for a minimum of 5 years on approval from the Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

## **20 Regulatory Considerations**

### **20.1 Ethical and governance approval**

This protocol has approval from a REC that is legally “recognised” by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review of a study with a lead site in Wales, i.e. Health and Care Research Wales Permissions Co-ordinating Unit (HCRW PCU).



Approval will be obtained from the host care organisation, Velindre University NHS Trust, who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

## 20.2 Data Protection

The Sponsor, Velindre University NHS Trust, will act as sole data controllers for the trial. Cardiff University and the participating site, VCC, will act as data processors.

The data controller will preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2018.

All source derived data will be stored and processed indefinitely under the legal basis 'task in the public interest' and in line with Cardiff University and Velindre University NHS Trust policies, UK REC guidance, and GDPR 2018 regulations.

Personal data collected from Healthcare Workers for the purposes of WP3 will be stored securely for a maximum of 12 months from the date of collection and destroyed immediately after the discussion group, following CTR SOP data protection Policies. Personal data collected by the VPLG for the purposes of WP1 will not be transferred from the VPLG to the CTR.

## 20.3 Indemnity

**Non-negligent harm:** This trial is an academic, investigator-led and designed trial sponsored by Velindre University NHS Trust and coordinated by the CTR. The CI, PI and CTR do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and therefore cannot offer any non-negligent harm indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

**Negligent harm:** In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the trial. Where NHS employees are responsible for the design of a trial, indemnity cover will also be provided for negligent harm arising

from the trial design. Velindre University NHS Trust does not accept liability for any breach in the other NHS Organisations duty of care, or any negligence on the part of employees of these NHS Organisations.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

## **20.4 Trial sponsorship**

The trial is being sponsored by Velindre University NHS Trust. The Trust shall be responsible for ensuring that the trial is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996).
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation (2016).
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the CI, PI, host site (VCC) and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type [29].

## **20.5 Funding**

This trial has been funded by a Tenovus iGrant and a Velindre University NHS Trust Charitable Funds grant. Sight is supplying the OLO System for free. The trial will be adopted into the CTR trial portfolio and considered for the Health and Care Research Wales (HCRW) trial portfolio.

## **21 Trial management**

### **21.1 Work Packages Group Leads**

The study will comprise four related work packages (WP) as specified in section 6. Each WP will be implemented by a defined WP group and lead. Each group will be responsible for the day-to-day conduct of their individual work package and will meet either weekly or monthly as appropriate to discuss the day-to-day issues that arise from the work package. Important discussions from each group will be relayed via the WP lead to the Trial Management Group (TMG) via the Trial Manager who will have the overall responsibility of co-ordinating all four WP.

### **22.2 Trial Management Group (TMG)**

The TMG will consist of the CI, Co-Investigators, Trial Manager, WP leads, key WP group members, a PPI research partner, and a qualitative research advisor. The CI will act as the Chair of the TMG. The role of the TMG will be to help set up the trial by providing specialist advice, input to and comment on trial procedures and documents (e.g. Protocol). They will also advise on the promotion and running of the trial and deal with issues that arise. The group will normally meet at least once a quarter during the 12-month study period, and more frequently during the initial set up phase if required. TMG members will be required to sign up to the remit and conditions as set out in the TMG/EC Charter [39] which will be filed in the TMF.

### **22.3 Executive Committee (EC)**

The trial will be overseen by an Executive Committee (EC) consisting of the Chief Investigator, the Statistician, the Trial Manager, the WP leads, an independent statistician, an independent clinician, and a PPI research partner. The independent Clinician will act as the chair of the EC. The purpose of the EC is to manage, steer, and monitor the safety and data integrity of WP1-3 in a cohesive manner to ensure delivery of the study within the planned milestones timeframes and resources. The EC will monitor the study according to the Trial Monitoring Plan which will be filed in the TMF. The EC will meet at least twice during the study, once after approximately half of the participants have been recruited to WP1 and again before the end of the 12 months study period. EC members will be required to sign up to the remit and conditions as set out in the EC Charter which will be filed in the TMF. EC members will be required to sign up to the remit and conditions as set out in the TMG/EC Charter [39] which will be filed in the TMF.

## **22.4 Trial Steering Committee (TSC)**

Due to the non-CTIMP design and low risk of this trial, it is not felt necessary to have an independent TSC. The EC will be responsible for steering the study.

## **22.5 Independent Data Monitoring Committee (IDMC)**

Due to the non-CTIMP design and low risk of this trial, it not felt necessary to have an IDMC. The EC will be responsible for safety and data monitoring.

# **22 Quality Control and Assurance**

## **22.1 Monitoring**

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the ADVANCE trial. Low monitoring levels will be employed and will be fully documented in the ADVANCE Trial Monitoring Plan [40].

The PI should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

## **22.2 Audits & inspections**

The CI, PI, CTR and participating site organisations will permit trial-related monitoring, audits, REC/IRB review, and regulatory inspection(s), providing direct access to source data / documents. The trial may be participant to inspection by the REC as the regulatory body that approved the trial. The trial may also be participant to inspection and audit by Velindre University NHS Trust under their remit as Sponsor.

# **23 Publication policy**

A Publication Plan [41] will be drafted by the TMG to document publication requirements and activities. All publications and presentations relating to the trial will be authorised by the TMG.

## 24 References

1. [http://www.ncin.org.uk/cancer\\_type\\_and\\_topic\\_specific\\_work/topic\\_specific\\_work/main\\_cancer\\_treatments](http://www.ncin.org.uk/cancer_type_and_topic_specific_work/topic_specific_work/main_cancer_treatments)
2. El Turabi A, Abel GA, Roland M, Lyratzopoulos G. Variation in reported experience of involvement in cancer treatment decision making: evidence from the National Cancer Patient Experience Survey. Br J Cancer. 2013 Aug 6;109(3):780-7. doi: 10.1038/bjc.2013.316. Epub 2013 Jun 27. PMID: 23807170.
3. Neutropenic sepsis: prevention and management in people with cancer. NICE Clinical guideline CG151 Published 19 September 2012 and reviewed February 2014 and again February 2019 with no recommended changes. <https://www.nice.org.uk/guidance/cg151>
4. Kumar, A. (2011) Optimizing antimicrobial therapy in sepsis and septic shock. Crit Care Nurs Clin North Am. 23(1):79-97.
5. National Chemotherapy Advisory Group (NCAG) "Chemotherapy Services in England: Ensuring quality and safety" report published 22 August 2009.
6. <http://www.transformingcancerservices.wales/>
7. Ceris Stubbs Personal communication.
8. <http://www.horiba.com/pl/publications/readout/article/the-pentra-series-automated-hematology-analyzer-352/>
9. Woolley et al. (2017). A comparison Between the HORIBA Yumizen H500 Point-of-Care Hematology Analyzer With a 5-Part White Cell Differential and the HORIBA Pentra 120. Point of Care, Vol 16, Number 2, 89-91.
10. Boyland , D. and Ingram, L.. Poster: Evaluation of the Yumizen H500 FBC analyser and potential clinical improvements for point of care testing for paediatric patients groups.
11. Sight OLO Evaluation Report - Comparison with Beckman Coulter DxH900 at a Public Hospital
12. Sight OLO Evaluation Report - Comparison with Horiba ABX Pentra XL80 at a Private Hospital
13. Sight OLO Evaluation Report - Comparison with Sysmex XN1000 at a Main Lab
14. Sight OLO Evaluation Report - Comparison with Sysmex XN1000 at an Oncology Lab
15. Sight OLO Evaluation Report - Comparison with Sysmex XN2000 at a Children Hospital
16. ADVANCE Risk Assessment
17. ADVANCE Site Staff Delegation Log
18. ADVANCE Site Staff Roles and Responsibilities document
19. ADVANCE Self-Evident Correction Log
20. UKONS Acute Oncology Initial Management Guidelines Version 2.0 26 March 2018

21. Velindre Cancer Centre Neutropenic Sepsis Management SOP Version 3.1 2019
22. WP1: Screening Logs
23. WP2: Screening Log
24. WP3: Screening Log
25. WP1: ADVANCE Cohort 1 Device PIS ICF; WP1: ADVANCE Cohort 2 Device PIS ICF
26. WP2: ADVANCE Patient Carer Focus Group PIS ICF
27. WP3: ADVANCE Healthcare Worker Focus Group PIS ICF
28. ADVANCE Participant Withdrawal Form
29. OLO System Test Kit Package Insert
30. Sight Quality Control (QC) Material Package Insert
31. Sight OLO-U1 Operator's Manual
32. Prolance Max Flow Lancet or equivalent Package Insert
33. ADVANCE Patient Acceptability Survey
34. ADVANCE Safety Management Plan
35. ADVANCE SAE Case Report Form
36. ADVANCE Statistical Analysis Plan
37. ADVANCE Qualitative Analysis Plan
38. ADVANCE Data Management Plan
39. ADVANCE Trial Management Group / Executive Group Charter
40. ADVANCE Trial Monitoring Plan
41. ADVANCE Publication Plan

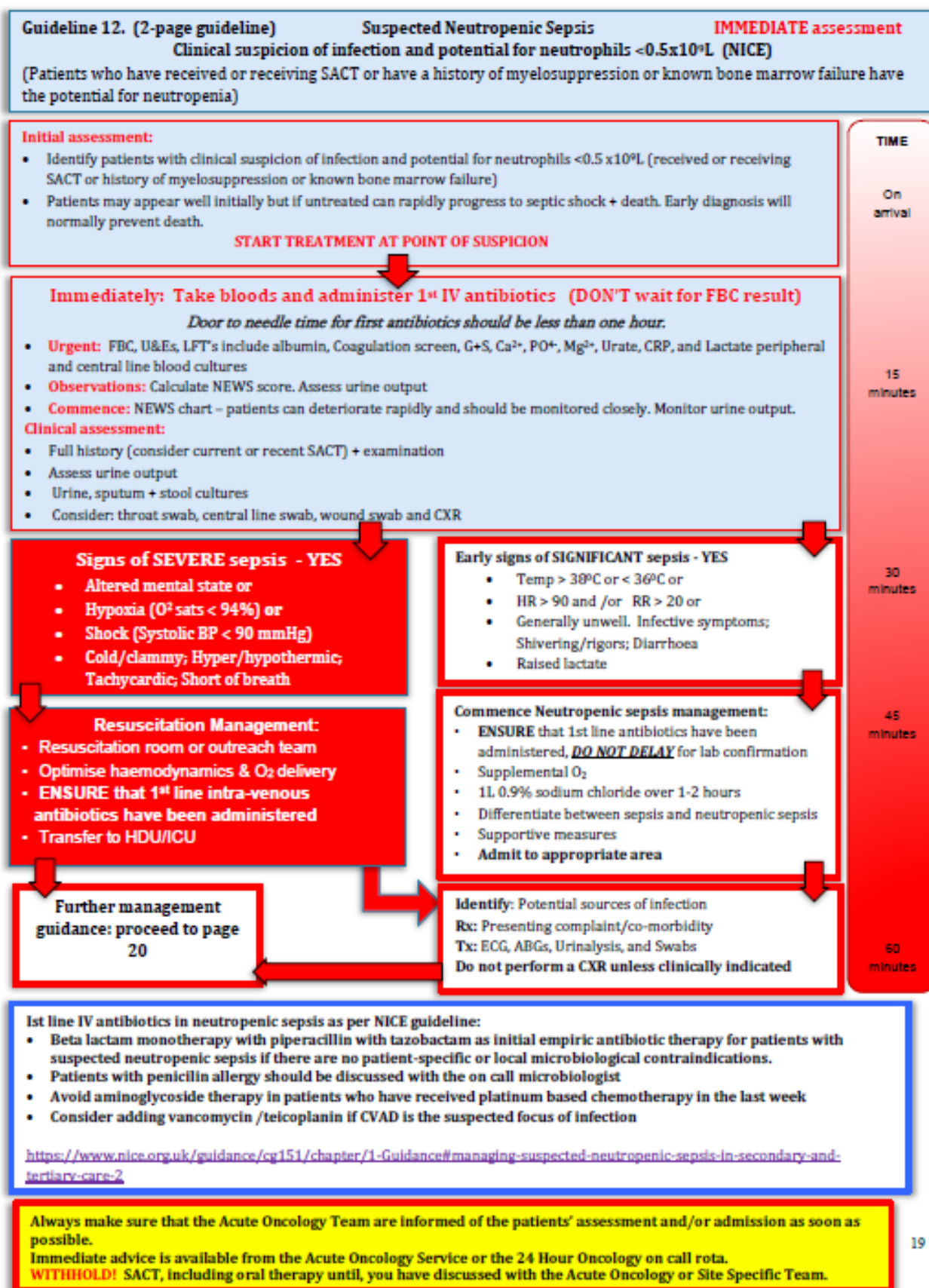
## 25 Appendices

### Appendix 1

- a) **UKONS Guideline 12 Suspected Neutropenic Sepsis**
- b) **UKONS 24-Hour Triage Tool - Assessment Poster**
- c) **UKONS 24-hour Trial Tool – Log Sheet**

Source: Pages 9-10 and 59-60 of UKONS Acute Oncology Initial Management Guidelines Version 2.0 26 March 2018 [20]. National guidelines regarding immediate management of patients diagnosed with cancer, including identification descriptions, questions and observations. The full guideline is available at <https://www.ukons.org/resources/>

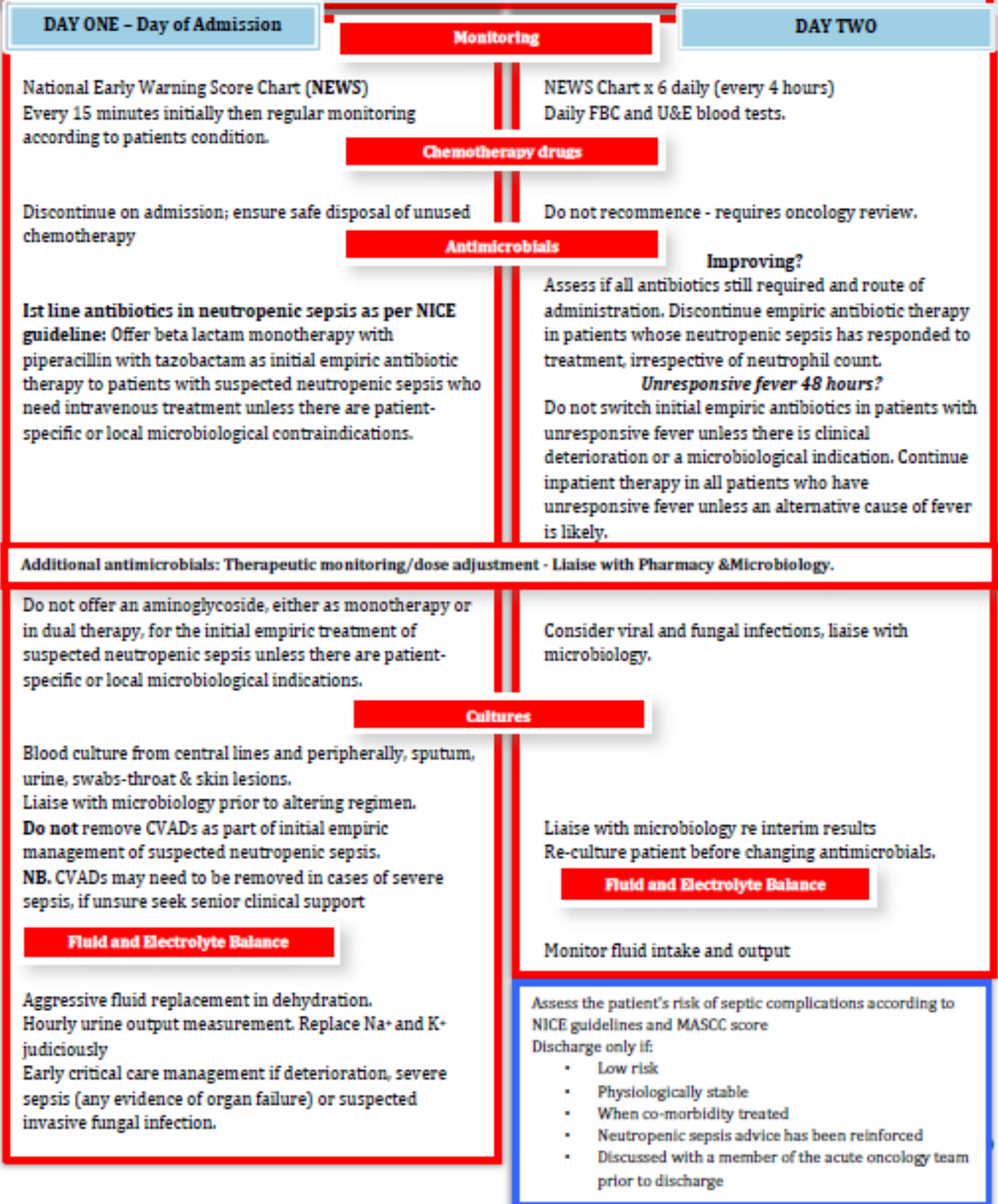
a) UKONS Guideline 12 Suspected Neutropenic Sepsis





**Guideline 12 continued. Suspected Neutropenic Sepsis**

- Subsequent treatment should occur in an environment where appropriate skills and expertise are available.
- The patient should be closely monitored and the patient's risk of septic complications frequently reassessed using a validated risk scoring system (NICE 2012).
- If the patient continues to deteriorate despite initial treatment their condition should be discussed urgently with a senior clinician.



b) UKONS 24-Hour Triage Tool - Assessment Poster

<b>ONCOLOGY/HAEMATOLOGY ADVICE LINE</b> <b>TRIAGE TOOL, VERSION 2</b> (NOVEMBER 2016)					
All Green = self care advice    1 Amber = review within 24 hours    2 or more amber = escalate to red    Red = attend for assessment as soon as possible					
<b>CAUTION!</b> Please note: This tool is for use by patients and carers only. It is not a substitute for medical advice. It is not intended to replace a GP or other healthcare professional. It is not intended to be used for patients with severe or life-threatening symptoms. It is not intended to be used for patients with symptoms that are not related to their cancer or its treatment.					
Toxicity/Symptom	0	1	2	3	4
<b>Fatigue</b> Is your energy or stamina low? Are you feeling more tired than usual? Have you lost weight or appetite? Have you been sleeping more than usual?	Green	Amber	Amber	Amber	Amber
<b>Chest pain</b> Is your chest pain new or worse than usual? Is it worse when you breathe, cough, or move?	Green	Amber	Amber	Amber	Amber
<b>Dyspnoea/shortness of breath</b> Do you have a cough or phlegm? Do you have a fever? Do you have any other symptoms?	Green	Amber	Amber	Amber	Amber
<b>Performance Status</b> Has there been a recent change in performance status?	Green	Amber	Amber	Amber	Amber
<b>Diarrhoea</b> How many days has it occurred for? How many times a day? Is it watery or bloody?	Green	Amber	Amber	Amber	Amber
<b>Constipation</b> How long has it lasted? What is the stool like?	Green	Amber	Amber	Amber	Amber
<b>Urinary Discomfort</b> Are you passing urine normally? Is there any pain or discomfort?	Green	Amber	Amber	Amber	Amber
<b>Nausea</b> How many days? What is the severity?	Green	Amber	Amber	Amber	Amber
<b>Vomiting</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Oral Discomfort</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Anorexia</b> What is the severity? How many days?	Green	Amber	Amber	Amber	Amber
<b>Pain</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Neurocognitive Function</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Cardiovascular Symptoms</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Edema</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Febrile</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Bleeding</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Weighting</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Double Eye Problems</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Painful Bladder Symptoms</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber
<b>Ear Infection</b> How many days? How many times?	Green	Amber	Amber	Amber	Amber

c) UKONS 24-hour Trial Tool – Log Sheet

HOSPITAL NAME / DEPT:		UKONS 24 HOUR TRIAGE LOG SHEET (v2 2016)																																																																												
<b>Patient Details</b>		<b>Patient History</b>																																																																												
Name:		Diagnosis:																																																																												
Hospital no.....		Male <input type="checkbox"/> Female <input type="checkbox"/>																																																																												
DOB.....		Consultant.....																																																																												
Tel no.....		Has the caller contacted the advice line previously Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																												
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Date..... Time.....																																																																														
Who is calling? .....																																																																														
Contact no.....																																																																														
Drop in: Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																														
<b>Reason for call</b> (in patients own words)																																																																														
Is the patient on active treatment? SACT <input type="checkbox"/> Immunotherapy <input type="checkbox"/> Radiotherapy <input type="checkbox"/> Other <input type="checkbox"/> Supportive <input type="checkbox"/> No <input type="checkbox"/>																																																																														
State regimen..... Are they part of a clinical trial Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																														
When did the patient last receive treatment? 1-7 days <input type="checkbox"/> 8-14 days <input type="checkbox"/> 15-28 days <input type="checkbox"/> Over 4 weeks <input type="checkbox"/>																																																																														
What is the patient's temperature? <input type="text"/> °C (Please note that hypothermia is a significant indicator of sepsis)																																																																														
Has the patient taken any anti-pyretic medication in the previous 4-6 hours Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																														
Does the patient have a central line? Yes <input type="checkbox"/> No <input type="checkbox"/> Infusional pump in situ Yes <input type="checkbox"/> No <input type="checkbox"/>																																																																														
<b>CAUTION!</b> Please note patients who are receiving or have received <b>IMMUNOTHERAPY</b> may present with treatment related problems at anytime during treatment or up to 12 months afterwards. If you are unsure about the patient's regimen, be cautious and follow triage symptoms assessment.																																																																														
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