Official Title	ThermoRad wIRA study: Prospective study to assess the real-world implementation of Thermotherapy using wIRA (water-filtered infrared A superficial hyperthermia) in addition to standard of care (SOC) palliative Radiotherapy (RT) in patients with inoperable or incurable cancers
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1 Protocol details

1.1 Title:

ThermoRad wIRA study: Prospective study to assess the real-world implementation of Thermotherapy using wIRA (water-filtered infrared A superficial hyperthermia) in addition to standard of care (SOC) palliative Radiotherapy (RT) in patients with inoperable or incurable cancers

Short title: Thermotherapy in addition to SOC palliative radiotherapy (ThermoRad wIRA)

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2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Dr. Anthony Kong

Signature Date

3 List of Abbreviations and Definitions

AE	Adverse events
APR	Annual progress report
AR	Adverse reactions
C&C	Capacity and capability
CAT	Complexity assessment tool
CI	Chief Investigator
CPS	Combined positive score
CR	Complete response
CRF	Case report form
cSCC	Cutaneous squamous cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer (EORTC)
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GSTT	Guy's and St Thomas NHS Foundation Trust
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HTA	Human Tissue Act
KCL	Kings College London
LIPS	Liquid immune profile-based signature
LRBC	Local recurrent breast cancer
MDT	Multidisciplinary team
NA	Not applicable
NASSS	Non-adoption, abandonment, scale-up, spread, and sustainability
NHS	National Health Service
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-L1	Programmed cell dealth ligand 1
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
PROM	Patient-reported outcome measure
QLQ	Quality of Life Core Questionnaire
QoL	Quality of life
R&D	Research and Development
RNA	Ribonucleic acid
RT	Radiotherapy
SAE	Serious Adverse Event
SOC	Standard of care
UK	United Kingdom
wIRA	Water-filtered infrared A

4 Summary/Synopsis

Trial Title	Prospective study to assess the real-world implementation of **Thermo**therapy using wIRA (water-filtered infrared A superficial hyperthermia) in addition to standard of care (SOC) palliative **Rad**iotherapy (RT) in patients with inoperable or incurable cancers	
Short Title	ThermoRad wIRA	
Protocol Version number and Date	Version 2.0, 12th May 2025	
IRAS Number	327431	
REC Reference	24/SC/0146	
Study Duration	3 years (2 years of recruitment followed by 12 months' follow-up period from the last participant recruited into the study)	
Sponsor name	KCL/GSTT	
Chief Investigator	Dr. Anthony Kong	
Funder	Dr. med. h.c. Erwin Braun Stiftung Foundation, Switzerland	
Medical condition or disease under investigation	Inoperable or incurable cancers with at least one lesion suitable for wIRA treatment, consisting of different cohorts of patients: 1) recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) 2) cutaneous squamous cell carcinoma (cSCC) not suitable for radical treatment 3) locally recurrent breast cancer (LRBC)	
	Objectives	**Endpoints**
Primary	To assess the real-world implementation of superficial hyperthermia using CE marked water-filtered infrared A (wIRA) in addition to palliative SOC radiotherapy	1. Quantitative: the total number and types of cancer patients successfully treated with the combination of superficial hyperthermia and palliative radiotherapy. 2. Descriptive: to evaluate the real-world implementation by the NASSS (non-adoption, abandonment, scale-up, spread, and sustainability) framework using NASSS-CAT (complexity assessment tool)
Secondary	1.To assess the best objective response rate (ORR) of the lesion(s) treated with combination of superficial hyperthermia with palliative radiotherapy	1. Best ORR: Defined as the proportion of patients achieving either a Complete Response (CR) or a Partial Response (PR). Complete Response (CR): Disappearance of all target lesions.

		Partial Response (PR): ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
	2.To determine the tolerability and safety profile of superficial hyperthermia in patients receiving SOC palliative radiotherapy	2. Local serious adverse events (SAEs) will be assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
	3.To evaluate the median local and global progression-free survival (PFS) and median overall survival (OS) of patients at 12 months after the last patient is recruited	3. Patients not experiencing an event (progression or death) will be censored at the time of the final analysis at the date last known to be alive and progression-free. Local: refer to the lesions treated by radiotherapy +/- superficial hyperthermia. Global: local and distant (non-treated lesions) PFS: Defined as the time from baseline to the first documented progressive disease (PD) or death from any cause, whichever occurs first. Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions or development of new lesions, with the date of progression recorded by a clinician in the patient's hospital records. OS: The time from the start of treatment to death from any cause.
	4. To assess the median duration of objective response and locoregional control rates of the treated lesion(s) at 6 and 12 months	4. Duration of Objective Response: Defined as the time from the first documented Complete Response (CR) or Partial Response (PR) to disease progression or metastasis. Locoregional Control Rate: The proportion of patients whose primary tumour site remains free from progression.

	5. To assess patient-reported outcomes measures (PROMs)	5. PROMs assessment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (QLQ-H&N43) (for HNSCC cohort) PROMs will be collected at baseline, during treatment (after the 3rd fraction of radiotherapy), 6 weeks post-treatment, 12-weeks post-treatment.
	6. To assess the differences in the efficacy between the lesion(s) treated with radiotherapy with hyperthermia with the lesion(s) treated with radiotherapy alone in those patients with at least 1 additional lesion that is not suitable for treatment with hyperthermia at 6 and 12 months	6. Percentage of best ORR, duration of response and disease control rates at 6 and 12 months in the lesion(s) treated with hyperthermia and radiotherapy versus lesion(s) treated with radiotherapy alone.
	7. To compare clinical outcome of patients treated with superficial hyperthermia in addition to SOC radiotherapy with historical control	7. Retrospectively collect data for historical cohort of similar cancer patients treated with SOC radiotherapy alone
Number of Subjects/Patients	• Up to 60 patients treated with superficial hyperthermia using water-filtered infrared hyperthermia (wIRA) hydrosun® TWH1500 treatment	
Patient cohorts	1) HNSCC i) Inoperable/incurable or recurrent/metastatic HNSCC with no previous radiotherapy treatment ii) Inoperable/incurable or recurrent/metastatic HNSCC with previous radiotherapy treatment (re-irradiation) 2) cSCC i) Inoperable/incurable or recurrent/metastatic cSCC with no previous radiotherapy treatment ii) Inoperable/incurable or recurrent/metastatic cSCC with previous radiotherapy treatment (re-irradiation) 3) LRBC locally recurrent breast cancer with previous radiotherapy treatment (re-irradiation)	

Study Type	Interventional study to implement superficial hyperthermia using wIRA machine in the real-world setting
Study endpoints	The end of the study definition is 12 months from the last participant recruited into the study after the 24-month recruitment period.
Main Inclusion Criteria	1. Patient with histologically confirmed incurable or inoperable cancers with disease [at least one superficial lesion(s) or lymph node(s)] suitable for hydrosun® TWH1500 treatment 2. Patient undergoing standard of care palliative radiotherapy (suitable with the pre-specified dose and fractionation in the protocol) 3. Aged ≥18 years old 4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 5. Patient with capacity to consent
Statistical Methodology and Analysis	This is a prospective study aiming to implement superficial hyperthermia using wIRA machine in the real-world setting and to recruit 15-20 patients in each disease cohort above (total = up to 60), which is the realistic target for two years.
Human Tissue and blood Samples (if applicable)	Peripheral bloods will be collected, and archival tissues will be requested to assess the peripheral and tissue immune markers. Other biological samples such as saliva, oral swab, urine, and stool samples may be collected for future translational research.
Data collected/storage (if applicable)	Patients' demographics, smoking and alcohol history, tumour characteristics, treatment details and responses, recurrences and survivals will be obtained from clinical record and recorded on paper Case Report Forms (CRFs).

5 Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and there are around 12 000 new cases in the UK each year (1). The most common causative agents include alcohol intake and smoking; however human papillomavirus (HPV) infection accounts for an increasing incidence of oropharyngeal cancer (2, 3). Patients presented with local disease can be offered treatment with surgery and/or radiotherapy with or without concurrent chemotherapy. Despite intensive treatment, 5-year survival rate remains poor, at approximately 50% for patients with high-risk features (HPV negative tumours and heavy smoking history) (4). Concurrent platinum chemotherapy with radical radiotherapy has been shown to increase survival in locally advanced HNSCC, but no survival benefit and poor tolerability was seen in those patients over 70 years old (5, 6), resulting in these patients being offered radiotherapy alone (with poorer outcomes). In addition, patients with locally advanced HNSCC who are older with co-morbidities are not fit or suitable for curative radical treatments, consisting of either primary surgery followed by adjuvant postoperative radiotherapy +/- chemotherapy or primary radiotherapy +/- concurrent chemotherapy. These patients

often end up receiving palliative radiotherapy alone. The focus of treatment for these patients is palliation to improve symptoms as well as to extend their life expectancy. Palliative radiotherapy treatment has been used successfully for both local control and palliation.

More recently these HNSCC patients are also treated with palliative immunotherapy if they are deemed fit to receive this treatment since the approval of pembrolizumab monotherapy in November 2020 in the UK as a result of the KEYNOTE-048 trial (7). In this study, it was shown that pembrolizumab monotherapy extended overall survival (OS) over the first-line chemotherapy in patients with HNSCC tumours with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) of ≥20% (HR = 0.61; p=0.007) and ≥1% (HR = 0.78; p=0.086) with favourable safety (7). This has resulted in the approval of pembrolizumab monotherapy for patients with HNSCC with CPS score ≥1%.

In addition to HNSCC, most patients with cutaneous SCC (cSCC) tend to be older with co-morbidities and many of them are not suitable or fit to undergo a course of curative treatment with a combination of surgery and/or radiotherapy. Cemiplimab is approved for use in patients with metastatic or locally advanced unresectable cSCC after a previous publication showed an objective response rate (ORR) of nearly 50% in these patients (8). In patients with locally advanced cutaneous SCC (cSCC) not suitable for curative surgery or radical radiotherapy, cemiplimab showed an antitumour activity with an objective response rate of 44% (of which complete response, CR, was 13%) and an acceptable safety profile (9). Thus, patients with incurable or recurrent cSCC not able to have curative treatment are often given palliative radiotherapy and/or cemiplimab since its approval in the UK.

The use of heat treatment in the management of malignant tumours has a long history and can be dated back to the ancient Greeks (10). Hyperthermia treatment involves the use of specific machines to apply heat, aiming to induce mild tumour heating up to a maximum temperature of 45°C (11, 12). It can further subdivide into three main categories including local, locoregional, and whole-body hyperthermia. Local heating is described as the process of heating the tumour volume, with no (or minimal) heating of normal surrounding tissue (11). It is widely evident that hyperthermia is a radiosensitiser through several mechanisms including reduction of hypoxia, increased vascular supply and inhibition of DNA repair (13-15). Moreover, it enhances the immune system and the synergistic effect with radiotherapy can lead to immunogenic cell death (16, 17).

Several technologies have been employed for the development of clinically approved superficial heating devices including microwave antenna, external infrared sources, ultrasound transducers and radiofrequency electrodes (11). The Hydrosun system (Hydrosun medizintechnik GmbH) uses water-filtered infra-red-A (wIRA) superficial hyperthermia technology to deliver contact free heating to large tumour areas (18). Despite the use of hyperthermia treatment in combination with other cancer

treatments such as radiotherapy and chemotherapy at many cancer centres across the world, its use has not been established in NHS settings. The main difficulties in introducing its use into routine clinical practise is the lack of expertise in its use as well as the lack of availability of clinically approved hyperthermia machines at any UK cancer centre. Guys Cancer Centre is the first centre nationally to introduce a CE marked hyperthermia machine (hydrosun®-TWH1500) for patient use in the NHS.

Patients presented with inoperable/recurrent disease usually have limited prognosis and any associated symptoms such as pain, discharge, infection, and bleeding significantly affect their quality of life. Several publications support the clinical use of hyperthermia with palliative radiotherapy in multiple tumour types (19). Datta et.al provides a summary of the clinical outcomes of 38 clinical trials across various tumour sites including breast, head and neck and skin melanoma comparing radiotherapy (1717 patients) versus thermoradiotherapy (1761 patients) and reported an overall clinical response of 54.9% in thermoradiotherapy groups vs 38.9% in the radiotherapy alone group (odds ratio: 2.3, 95% confidence interval 1.95–2.72, $p < 0.001$) (19). In a randomised phase 3 trial of patients with superficial measurable tumours treated with either radiotherapy alone or radiotherapy followed immediately by hyperthermia (42.5 degrees C, 45-60 min), a better CR rate was observed with a combination of radiotherapy and heat (62 and 67%) compared with irradiation alone (40 and 0%) in tumours less than 3 cm in diameter in the breast, trunk, and extremities despite no difference in overall CR between the two arms (20).

In head and neck cancer, a systematic review and meta-analysis comparing the efficacy of hyperthermia plus radiotherapy over radiotherapy alone showed an overall CR of 62.5% in the combination treatment versus 39.6% in the radiotherapy alone group (21). Moreover, a systematic review investigating the role of hyperthermia in the treatment of local recurrent breast cancer (LRBC) showed that the combination of hyperthermia with radiotherapy achieved a complete response rate of 60.2% compared to 38.1% for radiotherapy alone (22). However, most of the previous evidence is based on older hyperthermia and radiotherapy techniques, which have been disregarded by many oncologists as non-comparable to current standard of care.

The wIRA superficial hyperthermia system have been used in the EU and Switzerland for several years, which is proposed here, to treat patients with superficial tumours although most experience has been on locally recurrent breast cancers (LRBC) who had been previously and/or heavily irradiated. In a retrospective study of 73 LRBC patients, a CR rate of 61% was achieved in those with macroscopic disease (n=64) after being treated with re-irradiation 4 Gy per fraction per week for 5 weeks (4Gy x 5) with hyperthermia (18). They have further published another cohort of 201 patients treated with re-irradiation with hyperthermia in 2020 with similar efficacy and acceptable toxicities

(23). However, as most evidence has come from LRBC, there is uncertainty whether this real-world evidence is applicable to cutaneous SCC or HNSCC. In addition, there is uncertainty whether the weekly dose of 4Gy per week in combination with superficial hyperthermia using wIRA would be suitable for HNSCC or cSCC patients since the tumours may be more rapidly growing and this fractionation is not normally used in the standard of care. Furthermore, most of these patients also receive immunotherapy after palliative radiotherapy as part of the standard of care and there is uncertainty how this affects these patients receiving superficial hyperthermia and SOC palliative radiotherapy.

Through this prospective study, we hope to demonstrate the successful implementation of CE marked wIRA superficial hyperthermia in addition to SOC palliative radiation or re-irradiation in patients with inoperable or incurable cancers.

6. Aims and objectives:

- **Overall aim:**

This is a prospective study to assess the real-world implementation of superficial hyperthermia (wIRA) in addition to SOC palliative radiotherapy in cancer patients.

- **Patient's cohorts:**

1. HNSCC
   i. Inoperable/incurable locally advanced or recurrent/metastatic HNSCC with no previous radiotherapy treatment
   ii. Inoperable/incurable locally advanced or recurrent/metastatic HNSCC with previous radiotherapy treatment (re-irradiation)

2. cSCC in the head and neck region
   i) Inoperable/incurable locally advanced or recurrent/metastatic cSCC with no previous radiotherapy treatment
   ii) Inoperable/incurable locally advanced or recurrent/metastatic cSCC with previous radiotherapy treatment (re-irradiation)

3. LRBC
   i) Locally recurrent breast cancer with previous radiotherapy treatment (re-irradiation)

- **Primary objective:**

1. To assess the real-world implementation of superficial hyperthermia [using CE marked water-filtered infrared A (wIRA) machine] in addition to palliative SOC radiotherapy

- **Secondary objectives:**

1. To assess the best objective response rate (ORR)of the lesions treated with the combination of superficial hyperthermia (wIRA) and palliative radiotherapy
2. To determine the tolerability and safety profile of the combination treatment of superficial hyperthermia (wIRA) and palliative radiotherapy
3. To evaluate the median progression-free survival (PFS) and overall survival (OS) of patients
4. To assess the median duration of objective response and locoregional control rates at 6 and 12 months
5. To assess patient-reported outcome measures (PROMs) and quality of life (QoL) of patients using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) and head and neck module (QLQ-H&N35)
6. To assess the differences in the efficacy between the lesion(s) treated with radiotherapy with hyperthermia with the lesion(s) treated with radiotherapy alone in those patients with at least 1 additional lesion that is not suitable for treatment with hyperthermia
7. To compare clinical outcome of patients treated with combination of superficial hyperthermia and radiotherapy who may or may not undergo subsequent immunotherapy with the retrospective data of historical cohorts

- **Exploratory objectives/translational research:**

  Collection of samples such as archival tumour sample, fresh tumour biopsy/resected sample when available, blood (PBMC), and saliva, for translational research (see below).

- **Table 1: Objectives and endpoints**

	Objectives	**Endpoints**

Primary	To assess the real-world implementation of superficial hyperthermia using CE marked water-filtered infrared A (wIRA) in addition to palliative SOC radiotherapy as part of their standard of care (SOC)	1. Quantitative: the total number and types of cancer patients successfully treated with the combination of superficial hyperthermia and palliative radiotherapy. 2. Descriptive: to evaluate the real-world implementation by the NASSS (non-adoption, abandonment, and challenges to scale-up, spread, and sustainability) framework using NASSS-CAT (complexity assessment tool) [ξ]
Secondary	1.To assess the best objective response rate (ORR) of the lesion(s) treated with (1) combination of superficial hyperthermia with palliative radiotherapy; (2) radiotherapy alone	1. Best ORR: Defined as the proportion of patients achieving either a Complete Response (CR) or a Partial Response (PR). Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
	2.To determine the tolerability and safety profile of superficial hyperthermia in patients receiving SOC palliative radiotherapy	2. Local adverse events (AEs) and adverse reactions (ARs) will be assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
	3.To evaluate the median local and global progression-free survival (PFS) and median overall survival (OS) of patients at 12 months after the last patient is recruited Local: refer to the lesions treated by radiotherapy +/- superficial hyperthermia. Global: local and distant (non-treated lesions)	3. PFS: Defined as the time from baseline to the first documented progressive disease (PD) or death from any cause, whichever occurs first. PD: At least a 20% increase in the sum of diameters of target lesions or development of new lesions, with the date of progression recorded by a clinician in the patient's hospital records. OS: The time from the start of treatment to death from any cause. Patients not experiencing an event (progression or death) will be censored at the time of the final analysis at the date last known to be alive and progression-free.
	4. To assess the median duration of objective response and locoregional control rates of the treated lesion(s) at 6 and 12 months	4. Duration of Objective Response: Defined as the time from the first documented Complete Response (CR) or Partial Response (PR) to disease progression or metastasis.

		Locoregional Control Rate: The proportion of patients whose primary tumour site remains free from progression.
	5. To assess patient-reported outcomes measures (PROMs)	5. PROMs assessment using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (QLQ-H&N43) (for HNSCC cohort) PROMs will be collected at baseline, during treatment (after the 3rd fraction of radiotherapy), 6 weeks post-treatment, 12-weeks post-treatment.
	6. To assess the differences in the efficacy between the lesion(s) treated with radiotherapy with hyperthermia with the lesion(s) treated with radiotherapy alone in those patients with at least 1 additional lesion that is not suitable for treatment with hyperthermia	6. Percentage of best ORR, duration of response and disease control rates at 6 and 12 months in the lesion(s) treated with hyperthermia and radiotherapy versus lesion(s) treated with radiotherapy alone.
	7. To compare clinical outcome of patients treated with superficial hyperthermia in addition to SOC radiotherapy with historical control	7. Retrospectively collect data for historical cohort of similar cancer patients treated with SOC radiotherapy alone

[ξ]Descriptive primary endpoint: evaluation of the real-world implementation by the NASSS-CAT

Introduction of the new technology into the NHS can be very complex and the process of which cannot be easily captured by the traditional clinical trial endpoints. To this end, the non-adoption, abandonment, scale-up, spread, and sustainability (NASSS) framework allows the description of the complexity in real-world implementation of new technology consisting of six domains including (a) the condition or illness, (b) the technology, (c) the value proposition, (d) the adopter system, (e) the health care organization(s), and (f) the wider system (especially regulatory, legal, and policy issues). The seventh domain is cross-cutting, considering how all these domains interact and emerge over time (27). Extending the NASSS framework and building on a complexity assessment tool (CAT), four NASSS-

CAT tools were previously developed to apply the complexity principles to evaluate the introduction of technology in healthcare setting (28). These includes NASSS-CAT SHORT, NASSS-CAT LONG, NASSS-CAT PROJECT and NASSS-CAT INTERVIEW (see appendix). We will use these tools to evaluate the descriptive part of the primary endpoint of this study.

7. Study design & Flowchart

- **Study design**

This is a prospective study to assess the real-world implementation of superficial hyperthermia (wIRA) in combination with SOC palliative radiotherapy in cancer patients not suitable for radical treatment and have superficial lesion(s) suitable for wIRA treatment. All eligible patients will be recruited in the study by the clinical team following discussion with the chief investigator or the designated clinical sub-investigator. Patients will be consented for palliative radiotherapy as per standard treatment. The radiotherapy dose delivered will be clinician's choice based on SOC table 1 schedules.

Table 2: Schedule of radiotherapy and hyperthermia

Palliative radiotherapy (Primary vs Re-irradiation)	Dose	Fractions	Radiotherapy	Hyperthermia
Primary or Re-irradiation (previous standard palliative dose)*^	27Gy	6	Twice per week	Once per week
Re-irradiation (previous radical dose)*^	20Gy	5	Once a week (up to 5 weeks)	Once per week
Primary or Re-irradiation (previous standard palliative dose)*^	20Gy	5	Daily over 1 week	Twice per week
Re-irradiation (previous radical or palliative dose)*^	20Gy	10	Daily over two weeks	Twice per week
Primary or Re-irradiation (previous standard palliative dose)*^	36Gy	6	Once a week	Once per week

*The combined dose from previous RT and proposed RT fractionation will not exceed tolerance dose for critical organs (assuming recovery if necessary, as per routine clinical practice). If completing the full radiotherapy schedule would result in exceeding the tolerance dose to critical organs, treatment may be administered on a weekly basis until the tolerance threshold is reached.

^The combined dose from previous RT and proposed RT fractionation will not exceed tolerance dose for critical organs (assuming recovery if necessary, as per routine clinical practice) and the combined dose to soft tissue of the irradiated area will not exceed 70Gy in equivalent 2Gy per fraction (without assuming recovery).

The patients will receive hyperthermia either once a week or twice a week (as listed in Table 1) using hydrosun® TWH1500 with palliative radiotherapy. The patients will receive hyperthermia treatment for 1 hour before going for palliative radiotherapy as per standard of care. For patients who will undergo 27Gy/6#, they will receive hyperthermia once a week for three weeks during the course of palliative radiotherapy. For patients undergoing 20Gy/5# over five weeks or 36Gy/6# over six weeks, they will receive hyperthermia once a week. For patients undergoing 20Gy/5# over one week or 20Gy/10# over two weeks, they will receive hyperthermia two times per week during their treatment.

Most of the HNSCC patients will be suitable for palliative pembrolizumab (if the tumours are CPS≥ 1) and the cSCC patients will be suitable for cemiplimab if they have an ECOG performance status ≤1. We would aim to start palliative pembrolizumab within 6 weeks (+/- 2 weeks) of completing palliative radiotherapy if patients are deemed to be suitable and fit for this treatment as part of the standard of care. LRBC patients will undergo systemic treatments as per standard of care according to their previous treatment histories and breast cancer subtypes.

Patients will be assessed during their treatment for toxicities, and rate of adverse events will be assessed by CTCAE version 5.0. Follow-ups and assessment of response will be done as per standard of care.

When appropriate, we will aim to collect biological samples from each patient for translational research (see below) including archival tumour sample, fresh tumour biopsy or resection sample when available, blood samples at different time intervals before, during and after their treatments as well as saliva and mouth swab at the same time points when appropriate. The samples will be analysed to further assess the tumour microenvironment, the peripheral immune response and to identify predictors of treatment response.

For all patients, blood samples will be collected at baseline (at time of consent), before the first round of hyperthermia/radiotherapy treatment*, after the first round of hyperthermia/radiotherapy

treatment**, 6 weeks (+/- 2 weeks)*** post hyperthermia/radiotherapy, 12 weeks (+/- 2 weeks)*** post hyperthermia/radiotherapy, and at the first disease progression post hyperthermia/radiotherapy. Additionally, for those patients who will subsequently undergo anti-PD1/PD-L1 checkpoint inhibitor therapy (immunotherapy) as part of the standard of care, we will collect blood samples at immunotherapy baseline, 3 weeks (+/- 2 weeks) post-immunotherapy baseline, 6 weeks (+/- 2 weeks) post-immunotherapy baseline and at the first disease progression post-immunotherapy baseline. Other samples for translational research will be collected on clinician's discretion and up to a total of six times. As a standard of care, we routinely collect patient reported outcomes to assess toxicity to radiotherapy treatment thus we will continue to collect for this study.

* May be omitted if baseline bloods have been obtained. Omittance would occur due to logistical issues (i.e., difficult to arrange with the participant).

** This could usually be done after 3rd fraction of radiotherapy (if not possible, aim for 4th fraction of RT).

*** This allows for flexibility; due to the nature of the study, it may be that logistically issues make it difficult to arrange precisely at the exact timepoint.

5.1 Schedule of events

	Screening (Visit 0)	Baseline (Visit 1)	Pre-HT (Visit 2)	Post-HT/RT (Visit 3)	6 weeks post HT/RT (Visit 4)	12 weeks post HT/RT (Visit 5)	Disease progression (Visit 6)	IO baseline (Visit 7)	IO – 3wks (Visit 8)	IO-6wks (Visit 9)	IO-disease progression (Visit 10)	12 months post HT/RT
Eligibility criteria	X											
Participant information	X											
Informed consent		X										
Medical record monitoring		X	X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30		X		X	X	X						
EORTC QLQ H&N35		X		X	X	X						
Sample collection: blood		X	X*	X	X	X	X	X	X	X	X	
Sample collection: saliva		X	X*	X	X	X	X	X	X	X	X	

*This may be omitted if baseline measures were collected. Omittance may occur due to logistical issues (i.e., difficult to arrange with the participant)

Abbreviations: HT, hyperthermia; IO, Immunotherapy; RT, radiotherapy.

- **Treatment visits**

This is an interventional study to implement superficial hyperthermia in the real-world setting, and the patients will continue their clinical visits and follow-up as per normal standard of care. We will obtain the treatment outcome from medical records of patients. It will be during patients' SOC visits that we will collect biological samples and assess PROMs. All patients will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30). Additionally, the HNSCC cohort will also be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module. PROM assessments will take place during the same timepoints as biological sample collection, with the last PROM assessment taking place at 12 weeks post radiotherapy.

8. Subject selection

We will have the following cohorts of patients undergoing standard of care treatments, which we plan to include 15 to 20 patients in each disease cohort* and up to 60 patients in total:

1. **HNSCC cohorts**
   i. Inoperable/recurrent HNSCC with no previous radiotherapy treatment
   ii. Inoperable/recurrent HNSCC with previous radiotherapy treatment (re-irradiation)
2. **cSCC cohort**
   i. Inoperable/recurrent cSCC with no previous radiotherapy treatment
   ii. Inoperable/recurrent cSCC with previous radiotherapy treatment (re-irradiation)
3. **LRBC cohorts**
   i. Inoperable locally recurrent breast cancer with previous radiotherapy treatment (re-irradiation)

* The number of participants may vary between each group

- **Subject inclusion criteria**

1. Patient with histologically confirmed incurable or recurrent cancers with disease [at least one superficial lesion(s) or lymph node(s)] suitable for hydrosun® TWH1500 treatment
2. Patient suitable for SOC palliative radiotherapy or re-irradiation with one of the pre-specified palliative radiotherapy dose and fractionation (Table 1 above)
3. Aged ≥18 years old
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
5. Capacity to consent

- **Subject exclusion criteria**

1. No superficial tumour lesion or lymph node that is suitable for hydrosun® TWH1500 treatment
2. Patients are not suitable for one of the pre-specified palliative radiotherapy dose and fractionation (table 1 above)
3. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

- **Collection of biological samples for translational research**

We propose to develop a detailed investigation of total immune profile of patients following palliative radiotherapy +/- superficial hyperthermia to tumour lesion(s). Some of these patients may subsequently undergo palliative anti-PD1 or anti-PDL1 checkpoint antibody as part of the standard treatments. Understanding the immune responses to various treatments will help us to stratify and optimize patients' treatments and to combine different treatment modalities in a personalized manner. We also aim to uncover prognostic and predictive biomarker that could help to deliver a more personalized treatment in cancer patients undergoing palliative radiotherapy with superficial hyperthermia who may or may not subsequent anti-PD1 antibody as part of the standard of care.

We will assess peripheral immune responses as well as free and vesicular Hsp70 in the bloods from patients undergoing treatment at baseline and post-treatments:

1) palliative radiotherapy (RT) + hyperthermia: baseline, pre-hyperthermia treatment, post-hyperthermia/radiotherapy treatment (post-third or fourth fraction of RT), 6 weeks (+/- 2 weeks) post hyperthermia/radiotherapy, 12 weeks (+/- 2 weeks) post hyperthermia/radiotherapy and at the first disease progression post hyperthermia/radiotherapy.

2) For patients who will subsequently undergo anti-PD1/PD-L1 checkpoint inhibitor: baseline immunotherapy, 3 weeks (+/- 2 week) post-baseline immunotherapy, 6 weeks (+/- 2 weeks) post-baseline immunotherapy and at the first disease progression post immunotherapy. We will obtain whole blood and isolate PBMC from patients' blood and high parameter immune profile will be investigated with CyTOF (Mass Cytometry). In addition, we will assess free and vesicular serum and plasma Hsp70 from the patients, which will be correlated with the Hsp70 expression in tumour tissues and tumour infiltrating CD561 NK cells in formalin-fixed paraffin embedded (FFPE) tumour specimens (24-25). We will also assess immune markers on the diagnostic paraffin-embedded tissues (pre-treatment + post-treatment or post-recurrence if available) from the same cohort of patients. The peripheral immune responses will be correlated with the results done on tumour immune markers using Imaging Mass Cytometry. We will process additional blood samples according to the SOP

provided by Prof. Udo Gaipl for parallel biomarker work on liquid immune profile-based signature (LIPS) (26). In addition, blood samples will be collected for other translational research including assessment of ctDNA at the above time points. We will aim to collect blood samples at the same time that the patients are having blood tests at GSTT as part of the standard procedures or occasionally as an additional procedure in the time points above. On each occasion, we will take up to 40ml of blood. We may also ask them to donate other samples such as saliva, oral swab, urine or faeces for future research at the same time points above. The blood samples and any available fresh samples collected will be transported from Guy's Hospital (by foot) to Dr. Kong's laboratory at Guy's site at KCL. Translational research may be conducted for up to 5 years after the recruitment period.

9. Study procedures

- **Subject recruitment**

  - **Method of recruitment**

All eligible candidates will be identified and screened for eligibility criteria from the relevant tumour multidisciplinary team (MDT) and/or oncology clinics, and the initial approach to the potential participants will be made by the direct care team members. All cases will be discussed with the lead hyperthermia consultant (Dr Anthony Kong) or designated clinical sub-investigator prior to consent to the study. Participating patients should aim to start treatment as per usual standard of care.

  - **Payment**

The participants will not be paid for this study since patients will not be required to have additional visits other than their standard of care visit.

  - **Informed consent**

This study will initially be opened at Guy's and St Thomas' NHS foundation trust. Additional centres (including those in the overseas) may be opened later after appropriate ethical approval and funding is obtained in the respective country and centre. The Principal Investigator (PI) retains overall responsibility for the conduct of research at participating site with delegation of duties to appropriate clinical sub-investigators (e.g., clinical fellow), which includes the taking of informed consent of participants at their site with the processes below:

- Checking the inclusion and exclusion criteria
- A discussion with the potential participant about the research including the nature and objectives of this study and possible risks associated with their participation

- Patient information leaflet and consent form will be given to patients, usually at least 24 hours before consent
- Potential participants will be given the opportunity to ask questions
- Assessment of the mental capacity for the participants to consent will be performed by either the PI or the appropriate clinical sub-investigators. The PI will ensure that any person delegated the responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

To promote equitable representation and improve the generalizability of study findings, this research is committed to including non-English speaking participants. The consent process for the ThermoRad wIRA study is conducted independently from the standard radiotherapy consent process at Guy's Hospital. In accordance with institutional policy, all non-English speaking participants must be consented for radiotherapy in the presence of a GSTT-licensed interpreter. To ensure accurate understanding during the ThermoRad wIRA consent process, we will endeavour to implement one of the following procedures:

1. Pre-consent translation and telephone interpretation: A family member will be present in person to assist with translating the pre-consent discussion. During the formal consent process, a GSTT-qualified interpreter will be contacted via telephone to ensure the participant comprehends all study-related information. Both the participant and the accompanying family member will sign the consent form, and the name of the telephone interpreter will be recorded by the consenting clinician on the form.
2. Reinforcement during radiotherapy consent: During the radiotherapy consent appointment, the GSTT-licensed interpreter present will be asked to review the ThermoRad wIRA consent information with the participant to confirm understanding of the study and consent previously obtained.

- **Translational research**

Participants will be asked to give generic consent for their samples, derived organoids and/or cell lines and linked data to be transferred and used in future research. This includes the transfer and use of samples/data to KCL and its partners including the commercial sector and overseas organisations. Based on this consent, archival tissue, blood, saliva, oral swab, urine and stool samples will be collected and stored at Guy's and St Thomas' head and neck biobank during the study; and will be

stored beyond the ethical approval date of the project and stored under the custodial of Dr. Cheryl Gillet (HTA licence 12121; Licence Holder Cheryl Gillet) if the patients sign an additional biobank consent. All material will be handled in accordance with the Human Tissue Act 2004 and other relevant legislation relating to the use of cell lines. Specific agreements will be put in place as required by the Sponsor including material transfer agreements where necessary.

- **Withdrawal of consent**

The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Patients will be made aware of the terms and conditions around withdrawal. If a patient withdraws from the study, the research team can retain any biological samples and DNA/RNA samples up until the time of the patient's withdrawal if the patient agrees. Any unused samples taken for research purpose can be destroyed if patients request to do so. Any demographic and medical information already provided or results from tests already performed on their samples will continue to be used in the study, however no further data or sample collection will be performed. If a patient consents to the study but subsequently lose the capacity to consent during the study, he/she will be withdrawn from the study. However, we will retain and make further use of any identifiable data and collected tissues. We can destroy any unused samples taken for research purpose upon the request from the patient or the next of kin. We will also stop taking any further blood or other samples from the patient although we would like to continue collecting follow-up information from the hospital record and/or GP in regard to patients' disease status and survival outcome.

- **Screening Procedures**

No extra screening investigations are needed for this study since this is a real-world implementation study. Patients will undergo routine standard of care investigations and treatments apart from consenting to this study and for their samples to be used for translational research during their routine standard of care procedures

- **Schedule of assessments for each visit**

Patients will undergo assessments as per normal standard of care and the schedule will not be changed due to this study.

- **Follow-up procedures**

The follow-up procedures will be as per normal standard of care and the schedule will not be changed due to this study. We will obtain relevant clinical information from the medical records.

- **End of Study Definition**

The patient recruitment for the prospective study will initially be 24 months from the commencement of the study at coordinating site, Guy's and St. Thomas' NHS Foundation trust. Thereafter, the patients will be followed up for their long-term treatment outcome and survival as per normal standard of care. We will continue to obtain relevant information on patients' treatment and survival outcome from patients' medical records. The end of the study definition is 12 months from the last participant recruited into the study. We will assess whether the endpoints and outcomes are met at the end of the study, particularly the real-world implementation of superficial hyperthermia (using CE marked water-filtered infrared A (wIRA) machine) in addition to palliative radiotherapy and whether we are able to recruit the target number of patients.

We will submit the protocol for a major amendment towards the end of the study if the study is to continue for up to an additional 3 years of recruitment, providing further funding is obtained. Otherwise, we will analyse all data and produce the final study report at the end of third year.

The criteria for progression beyond the two-year recruitment period are set as below:

1. The study recruits well and reaches the target number of patients (up to 60 patients)

2. The study showed that superficial hyperthermia with wIRA could be implemented in the real-world setting and used in combination with palliative radiotherapy in cancer patients

3. Further funding is obtained to continue beyond the two-year recruitment period

10. Laboratories

Collected patients' samples from Guy's Hospital as part of translational research will be transferred to Dr Kong's laboratory at Kings College London for further processing. The samples will be pseudo-anonymised with sample IDs which can be linked to patients. The sample processing will be done by the research assistant appointed for the study and/or Dr. Kong's lab members and only those with KHP passport will have access to patients' confidential information. The samples will not be transferred or given to anyone without an MTA agreement. However, if there are any successfully generated organoids from any fresh samples, the anonymised organoids may be shared with collaborators. Based on the consent from patients, any other unused blood, saliva, oral swab, urine, and stool samples will be stored at Guy's and St Thomas' head and neck biobank beyond the ethics approval date of the project.

These samples can only be transferred or used if there is an MTA agreement in place. The samples will be stored for up to 5 years under the custodial of Cheryl Gillet (HTA licence 12121; Licence Holder Cheryl Gillet) for future analysis and possible future research. If the samples are not used by then, they will be destroyed according to the standard operating procedure of the biobank. Further details on the sample collection, processing, storage, and analysis will be provided in the laboratory manual.

- **Data Recording/Reporting**

All staff that would directly deal with human tissues or blood will undertake HTA training.

- **Sample Receipt/Chain of Custody/Accountability**

Handling of the samples upon arrival at the laboratory needs to be documented. Upon receipt of the samples, the laboratory should ensure that the physical integrity of these samples have not been compromised in transit. If it has, it is important that the study teams, as well as the sponsor, are informed of this. Upon receipt of samples laboratory staff should ensure that all samples are accounted as per the labeling. All samples received should be logged in an accountability log.

- **Sample transfer to sites outside the organization**

Individual informed consent will be obtained from the patients to specify whether they would agree for their samples to be transferred to collaborating third parties including overseas and commercial laboratories on behalf of KCL. This may include but not be limited to validation of research results.

The patient samples and derived organoids (with linked data) may be shared with collaborating laboratories, nationally or internationally, for the purposes of facilitating the research aims. Specific agreements will be put in place as required by the Sponsor including material transfer agreements where necessary. Any commercialisation of the results of this study will be specified in contractual arrangements between parties where necessary and participants will be informed that they would not benefit financially.

11. Assessment of Safety

This is a real-world implementation study, and the patients participated in this study will undergo superficial hyperthermia in addition to SOC palliative radiotherapy. Hyperthermia treatment has not shown to significantly increase acute or late toxicities compared to radiotherapy alone. In a summary of the clinical outcomes of 38 clinical trials across various tumour sites using hyperthermia did not report any significant increase in reported acute or late toxicity with the addition of hyperthermia (19). Similarly, in a systematic review of the use of hyperthermia in addition to radiotherapy for head and neck cancer (20), did not report any worsening toxicities from the addition of hyperthermia, apart

from one study reporting a 30% increase of thermal blisters however both older radiotherapy and hyperthermia techniques have been used (22). The Hydrosun system has been evaluated in superficial breast cancer re-irradiation with no acute grade 2-4 toxicities been observed, including no burning with blistering (18). We will collect safety profile data from the patients undergoing superficial hyperthermia with SOC palliative radiotherapy in this study.

- **Procedures for Recording and Reporting Adverse Events**

No serious adverse events (SAEs) are expected to occur due to hyperthermia alone, but it can sensitize radiotherapy. For patients undergoing palliative radiotherapy and hyperthermia, they will be followed up by their treating clinicians as per normal practice.

The HRA gives the following definitions for Safety Reporting (Research other than Clinical Trials of Investigational Medical Products (CTIMPs)) for UK Health Departments' Research Ethics Service (RES):

Serious Adverse Event (SAE) is defined as an untoward occurrence that:

a) Results in death; or
b) Is life-threatening; or
c) Requires hospitalization or prolongation of existing hospitalization or
d) Results in persistent or significant disability or incapacity; or
e) Consists of a congenital abnormality or birth defect; or
f) Is otherwise considered medically significant by the investigator.

In line with the study sponsor conditions and HRA guidance, if a SAE is discovered and thought to be related to superficial hyperthermia (+/- SOC palliative radiotherapy)**, the CI will immediately report upon knowledge of the event to the R&D Department within 24 hours**. I**f the SAE is considered to be related to** superficial hyperthermia (+/- SOC palliative radiotherapy) **and unexpected, it will also be reported to the relevant REC committee within 15 days of the** CI **becoming aware of the event. The HRA defines SAEs as related to the study if it involves the administration of any of the research procedures and unexpected as in that it was not listed in the protocol as an expected occurrence.** If the CI deems a SAE to be disease-related and not related to the superficial hyperthermia (+/- SOC palliative radiotherapy), the SAE will be documented but only reported in the final study report. Therefore, only SAEs that are localised to the site of hyperthermia (local adverse events) will be reported. **Participants will be monitored for SAEs for 6 weeks after completion of radiotherapy. All documentation relating to SAEs will be kept in the Trial Master File.**

12. Compliance and withdrawal

- **Subject compliance**

We will monitor the percentage of approached participants who consent to taking part in the study during the first year of recruitment.

- **Withdrawal/dropout of subjects**

We will monitor the percentage of participants who withdraw consent or drop out from the study after taking part. We will replace the subjects if necessary to make up the total target number of patients (n=30) as long as this is within the recruitment period.

- **Protocol compliance**

The patients will undergo routine treatments as per standard of care.

13. Data

- **Data management**

As this is a real-world implementation study, we will collect data from patients that are already available in the hospital record on patients' demographics, smoking and alcohol history, tumour characteristics including HPV status when applicable, proposed treatment plans. The patients' treatment details, treatment responses, progression and survivals will also be obtained from clinical record. They will be recorded on paper CRFs. Participant files and paper CRFs will be identified using a Participant Identification Number. Personal information will not be stored on CRFs. Screening and enrolment logs will be maintained by the research team. For enrolled participants, identifiable patient data will be stored in an Excel file for the purposes of gathering follow-up data. This file will password protected and stored on the KCL secured network, whereby access is only granted by the PI to named individuals.

Paper CRFs, consent forms and the Trial Master File will be stored in locked filing cabinets within the Dr. Kong's Office (KCL, New Hunt's House, London, UK). Data generated from laboratory processes related to the generation of PDOs and subsequent testing will be kept in the research laboratory. These data will be identified with the PIN and no personal data will be used in the lab records.

- **Data linkage**

If the participating patients have come from or will move to different health care providers, we will attempt to get either available archival tissues and/or data from the relevant health care providers

after sending them the relevant patients' consent forms. We may also go to the central national databases with a patient's NHS number to get clinical data if necessary.

14. Statistical considerations and additional participating sites

This is a prospective study to assess the implementation of wIRA superficial hyperthermia machine in the real-world setting and no formal power calculation is performed. The number of patients chosen for each cohort is the expected number of patients that we anticipate recruiting within 24 months based on the number of cancer patients that we treat at Guy's Cancer Centre. The study will initially commence as a single-site study at GSTT. Other UK sites may be added via a substantial amendment in due course if they acquire the same CE marked machine and would like to participate in the study. Consideration as to whether sites outside of the UK will be able to take part in the study will be considered in due course although this may not be possible due to the different health policy and the additional ethical approval requirement. The data from this prospective study will be used to calculate the sample size required if we extend the study beyond two years of recruitment or to plan a future interventional study, which will be submitted as a major amendment.

15. Ethical considerations

- **Research Ethics Committee (REC) review & reports**

Before the start of the trial, approval will be sought from an NHS REC for the trial protocol, informed consent forms, patient information sheet, and GP information letters.

Any amendments to the protocol or study documents will be reviewed by the Sponsor, sent to the REC for review and approvals. No changes will be implemented until approval has been received from the REC and approved by the Trust R&D department, if required.

All correspondence with the REC will be retained in the Trial Master File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator's will approve the annual report which will be submitted by the CI or delegate.

The CI will notify the REC of the end of the trial within 90 days of the end of the study. If the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

- **Peer review**

The study proposal was previously submitted to Braun Foundation for funding and the peer review process was undertaken by the committee and a conditional offer of funding (pending ethical approval) has been made.

- **Regulatory compliance**

The trial will not commence until a Favourable REC opinion is obtained along with HRA approval and confirmation of capacity and capability (C&C) from the GSTT R&D department.

16. Financing and Insurance

The study will be funded by Braun Foundation, and it is co-sponsored by King's College London and Guys and St Thomas' NHS Foundation Trust. The sponsors will, at all times, maintain adequate insurance in relation to the study. King's College London through its' own professional indemnity (Clinical Trials) & no-fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

King's College London employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

King's College London cannot offer indemnity for non-negligent harm.

17. Reporting and dissemination

The results of this trial will be submitted for publication in peer-reviewed journals. The manuscripts will be prepared by the chief investigator and co-investigators. The authorship will be determined by mutual agreement. A copy of the publication will be provided to the participants if interested and requested.

18. References

1. UK CR. Head and neck cancers statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers.

2. Haddad RI, Shin DM. Recent Advances in Head and Neck Cancer. New England Journal of Medicine. 2008;359(11):1143-54.

3. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261-9.

4. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. New England Journal of Medicine. 2010;363(1):24-35.

5. Pignon J-P, Maître Al, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiotherapy and Oncology. 2009;92(1):4-14.

6. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. The Lancet Oncology. 2010;11(1):21-8.

7. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, Jr., et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. The Lancet. 2019;394(10212):1915-28.

8. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. New England Journal of Medicine. 2018;379(4):341-51.

9. Migden MR, Khushalani NI, Chang ALS, Lewis KD, Schmults CD, Hernandez-Aya L, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol. 2020;21(2):294-305.

10. Hurwitz M, Stauffer P. Hyperthermia, radiation and chemotherapy: the role of heat in multidisciplinary cancer care. Semin Oncol. 2014;41(6):714-29.

11. Kok HP, Cressman ENK, Ceelen W, Brace CL, Ivkov R, Grull H, et al. Heating technology for malignant tumors: a review. Int J Hyperthermia. 2020;37(1):711-41.

12. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, et al. Hyperthermia in combined treatment of cancer. The Lancet Oncology. 2002;3(8):487-97.

13. Horsman MR, Overgaard J. Hyperthermia: a potent enhancer of radiotherapy. Clin Oncol (R Coll Radiol). 2007;19(6):418-26.

14. van den Tempel N, Horsman MR, Kanaar R. Improving efficacy of hyperthermia in oncology by exploiting biological mechanisms. Int J Hyperthermia. 2016;32(4):446-54.

15. Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, et al. The cellular and molecular basis of hyperthermia. Critical Reviews in Oncology/Hematology. 2002;43(1):33-56.

16. Frey B, Weiss EM, Rubner Y, Wunderlich R, Ott OJ, Sauer R, et al. Old and new facts about hyperthermia-induced modulations of the immune system. Int J Hyperthermia. 2012;28(6):528-42.

17. Repasky EA, Evans SS, Dewhirst MW. Temperature matters! And why it should matter to tumor immunologists. Cancer Immunol Res. 2013;1(4):210-6.

18. Notter M, Piazena H, Vaupel P. Hypofractionated re-irradiation of large-sized recurrent breast cancer with thermography-controlled, contact-free water-filtered infra-red-A hyperthermia: a retrospective study of 73 patients. Int J Hyperthermia. 2017;33(2):227-36.

19. Datta NR, Ordonez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and-/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev. 2015;41(9):742-53.

20. Perez CA, Pajak T, Emami B, Hornback NB, Tupchong L, Rubin P. Randomized phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors. Final report by the Radiation Therapy Oncology Group. Am J Clin Oncol. 1991;14(2):133-41.

21. Datta NR, Rogers S, Ordonez SG, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. Int J Hyperthermia. 2016;32(1):31-40.

22. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016;94(5):1073-87.23. Notter M et al. Combined wIRA-hyperthermia and hypofractionated re-irradiation in the treatment of locally recurrent breast cancer: evaluation of therapeutic outcome based on a novel size classification. Cancers 2020; 12: 606; doi:10.3390/cancers12030606.

23. Notter M et al. Combined wIRA-hyperthermia and hypofractionated re-Irradiation in the treatment of locally recurrent breast cancer: evaluation of therapeutic outcome based on a novel size classification. Cancers 2020; 12(3): 606.

24. Werner C et al. Hsp70 in liquid biopsies— a tumor-specific biomarker for detection and response monitoring in cancer. Cancers 2021;13(15):3706.

25. Stangl S et al. Heat shock protein 70 and tumor-infiltrating NK cells as prognostic indicators for patients with squamous cell carcinoma of the head and neck after radiochemotherapy: a multicenter retrospective study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). Int. J. Cancer 2018;142(9):1911-1925.

26. Zhou J et al. Prospective development and validation of a liquid immune profile-based signature (LIPS) to predict response of patients with recurrent/metastatic cancer to immune checkpoint inhibitors. Journal for ImmunoTherapy of Cancer 2021;9:e001845. doi: 10.1136/jitc-2020-001845.

27. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies. J Med Internet Res 2017;19(11):e367.

28. Greenhalgh T, Maylor H, Shaw S, Wherton J, Papoutsi C, Betton V, Nelissen N, et al. The NASSS-CAT Tools for Understanding, Guiding, Monitoring,

and Researching Technology Implementation Projects in Health and Social Care: Protocol for an Evaluation Study in Real-World Settings. JMIR Res Protoc 2020;9(5):e16861.

NASSS-CAT (SHORT)
IDENTIFYING COMPLEXITIES IN YOUR TECHNOLOGY PROJECT

The questions below help you think about the various complexities of your project and how they all interact. Use your responses and notes as the basis for a team discussion.

Name of your project:

……

1. THE ILLNESS OR CONDITION

Think about the illness or other condition that the technology is designed for – and what sort of person has that condition.

	Agree	*Disagree*	*Not applicable or don't know*
There are significant uncertainties about the condition e.g. poorly-defined, variable manifestations, uncertain course			
Many people with the condition have other co-existing illnesses or impairments that could affect their ability to benefit from this solution			
Many people with the condition have social or cultural factors that could affect their ability to benefit from the technology or service			
The population with the condition, and/or how the condition is treated, is likely to change significantly over the next 3-5 years			
SUMMARY: The condition has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

2. THE TECHNOLOGY

Think about the technology (e.g. a tool or piece of software), and how it might affect care.

	Agree	*Disagree*	*Not applicable or don't know*
There are significant uncertainties in what the technology is (e.g. it hasn't been fully developed yet)			
There are significant uncertainties in where the technology will come from (e.g. supply chain issues, substitutability)			
There are significant uncertainties about the technology's performance and dependability (e.g. bugs, crashing, cutting out)			
There are significant uncertainties about the technology's usability and acceptability (e.g. key people don't trust the data it provides)			
There are significant technical interdependencies			
The technology is likely to require major changes to organisational tasks and routines			

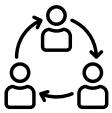
The technology (and/or the service model it supports) is likely to change significantly within the next 3-5 years			
SUMMARY: The technology has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

3. THE VALUE PROPOSITION

Think about what kind of value the technology might generate for different groups of people. ('Value' can be financial, such as profit, or non-financial, such as control of symptoms)

	Agree	*Disagree*	*Not applicable or don't know*
The commercial value of the technology is uncertain			
The value to the intended users (e.g. patients, clinicians) is uncertain			
The value to the healthcare system (e.g. from efficacy and cost-effectiveness studies) is uncertain			
The value to this particular healthcare organisation, given the current situation locally, is uncertain			
The technology could generate a negative value (costs are likely to outweigh benefits) for some stakeholders			
The value proposition is likely to change significantly over the next 3-5 years			
SUMMARY: The value proposition has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

4. THE INTENDED ADOPTERS



Think about who is intended to use the technology and what changes it will bring for them.

	Agree	*Disagree*	*Not applicable or don't know*
There is uncertainty about whether and how patients/citizens will adopt the technology [if applicable]			
There is uncertainty about whether and how front-line staff will adopt the technology			
There is uncertainty about the implications for people who might be indirectly affected by the technology			
There will be significant changes to individual users' perceptions of the technology over the next 3-5 years			
SUMMARY: There is significant complexity relating to intended adopters which is likely to affect the project's success	*Yes* ☐	*No* ☐	

5. THE ORGANISATION(S) IMPLEMENTING THE TECHNOLOGY

Some organisations are better at taking up innovations than others. What about yours?

	Agree	*Disagree*	*Not applicable or don't know*
The organisation's capacity to take on technological innovations is limited			
The organisation is not ready for this particular innovation			
The organisation would find it hard to commission/purchase the innovation			
The work needed to introduce and routinise the innovation has been underestimated and/or inadequately resourced			
The organisation(s) involved are likely to have significant restructurings or changes in leadership, mission or strategy over the next 3-5 years			
SUMMARY: There is significant complexity relating to one or more participating organisations which is likely to affect the project's success	*Yes* ☐	*No* ☐	

6. THE EXTERNAL CONTEXT FOR INNOVATION

Think about external conditions that could complicate adoption and spread of the innovation.

	Agree	*Disagree*	*Not applicable or don't know*
The political and/or policy climate is adverse			
Professional bodies are opposed to the innovation or don't actively support it			
Patient organisations and lobbying groups are opposed to the innovation or don't actively support it			
The regulatory context is adverse			
The commercial context is adverse			
Opportunities for learning from other (similar) organisations are limited			
Introduction of the technology/innovation could be threatened by external changes that impact on the organisation			
The policy, regulatory and economic context for this innovation is likely to be turbulent over the next 3-5 years			
SUMMARY: There is significant complexity relating to the external context which is likely to affect the project's success	*Yes* ☐	*No* ☐	

THINGS TO EXPLORE OR DISCUSS: List the key things in each domain that you would like to look up or discuss with other team members or wider stakeholders

The illness or condition	The technology	The value proposition
The intended adopters	The organisation	The external context

NASSS-CAT (PROJECT VERSION)
FOR MONITORING PROJECT COMPLEXITY OVER TIME

This version of the NASSS-CAT is intended to be used when you are setting up and running a specific project to implement a new technology in a health or care setting. You may be asked to complete it more than once as the project unfolds. Score one point for every 'agree' answer and add up the orange column. In the blue column, tick if you think this issue is going to get more complex in the next phase of the project. Note: this tool will only give you a semi-quantitative estimate because some aspects of a project will be more important than others.

	Agree	*Disagree*	*Not applicable or don't know*	*Likely to get more complex in next phase*
STRATEGIC COMPLEXITIES				
1. The vision and benefits for the project are not yet clear				
2. The fit between this technology and the organisation's mission and strategy is poor				
3. The business case for the work is unclear or contested				
4. The scope of the project is unclear or contested				
5. The work will have major knock-ons for other key projects and business-as-usual operations				
6. Success criteria are not yet explicitly set out and agreed by key stakeholders				
7. The project's success could be threatened by external changes that impact on the organisation				
TOTAL STRATEGIC COMPLEXITY SCORE	/7			/7

	Agree	*Disagree*	*Not applicable or don't know*	*Likely to get more complex in next phase*
TECHNICAL COMPLEXITIES				
1. The technology does not yet exist in a robust and dependable form				
2. The technology is unfamiliar to the project team				
3. The technology supply chain is not yet in place				
4. The technology cannot be installed until the system is upgraded (e.g. hardware, bandwidth)				
5. A key technology needs to be installed across multiple technical systems to achieve 'integration'				
6. Introducing the technology will require significant changes in care pathways and organisational routines				
7. Quality standards and regulatory requirements for using the technology in a health/care setting have not been fully defined (or key stakeholders don't know about them or accept them)				

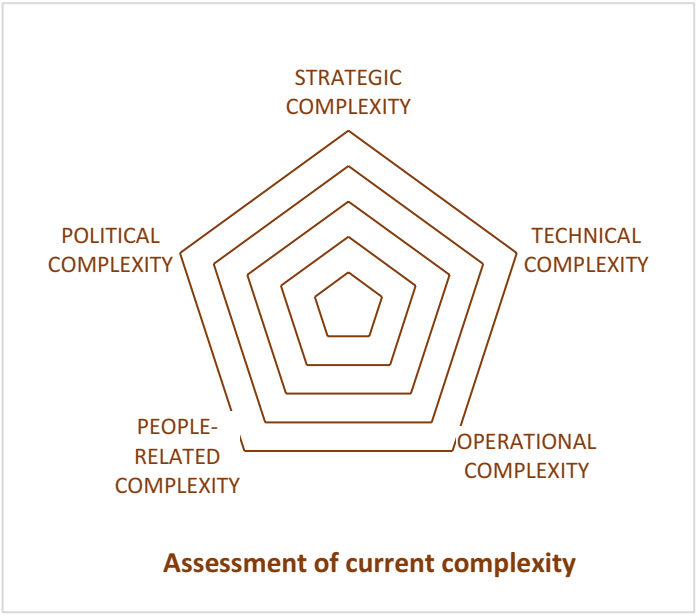
TOTAL TECHNICAL COMPLEXITY SCORE	/7			/7

	Agree	*Disagree*	*Not applicable or don't know*	*Likely to get more complex in next phase*
OPERATIONAL COMPLEXITIES				
1. A schedule and resource plan have not yet been defined				
2. The pace of the project (time to achieve key goals and milestones) seems unachievable				
3. The budget is insufficient for the task or there is limited flexibility in how the budget can be used				
4. Resources (e.g. test facilities, equipment) may not be available when needed				
5. Evaluation measures and metrics have not yet been agreed				
6. Accurate, timely and comprehensive data reporting will be difficult or impossible				
7. New management tools and data sources will be needed to guide, monitor and evaluate the project				
TOTAL OPERATIONAL COMPLEXITY SCORE	/7			/7

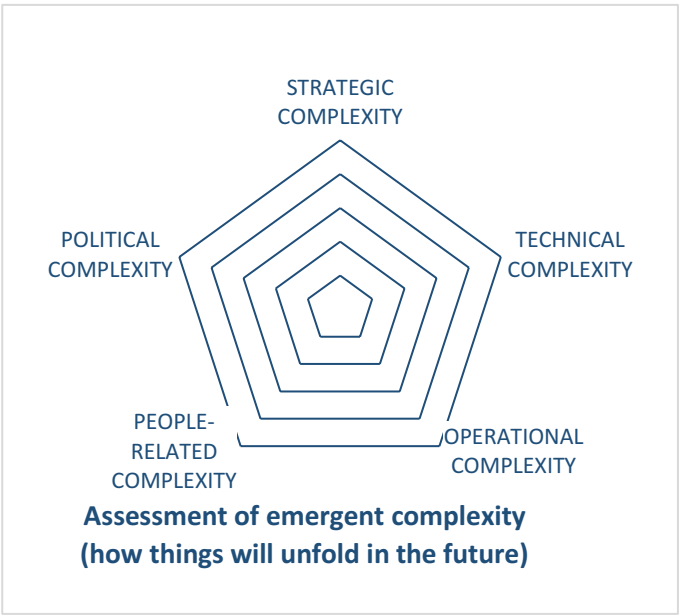
	Agree	*Disagree*	*Not applicable or don't know*	*Likely to get more complex in next phase*
PEOPLE-RELATED COMPLEXITIES				
1. The people leading the project are inexperienced in this kind of work				
2. The people leading the project do not have adequate control over project staff (e.g. no direct reporting)				
3. There are not yet sufficient people with the right skills available to participate in the project.				
4. There are no key people who are wholly allocated to the work for the project				
5. Lines of responsibility for tasks and deliverables are not yet defined				
6. Team members have limited confidence in the technology or do not fully understand how to use it				
7. Team members have limited motivation and are not yet functioning well as a team				
TOTAL PEOPLE-RELATED COMPLEXITIES	/7			/7

"POLITICAL" COMPLEXITIES	*Agree*	*Disagree*	*Not applicable or don't know*	*Likely to get more complex in next phase*
1. The work does not have a senior sponsor in the organisation who recognises its importance and helps negotiate its progress				
2. The senior management team in the relevant department does not fully support the work				
3. Substantial work will be needed to bring people on board and develop a shared vision for the change				
4. People beyond the core team don't understand the project or have unrealistic expectations for it				
5. People beyond the project team don't support the project or are not aligned or have insufficient time				
6. The core team does not have the authority to make decisions				
7. The work will require cooperation across sectors (e.g. health / social care)				
TOTAL "POLITICAL" COMPLEXITY SCORE	/7			/7

Plot your scores on the radar charts below to get a quick visualisation of the different complexities as assessed by you. The one on the left is your assessment of current complexity (orange columns above); on the right is your assessment of emergent complexity (blue columns above). Compare your radar charts with those made by your colleagues. Do your charts look the same? If not, where are the discrepancies and what explains these?



Assessment of current complexity



Assessment of emergent complexity (how things will unfold in the future)

NASSS-CAT (LONG VERSION)

ASSESSING AND HANDLING COMPLEXITY IN TECHNOLOGY PROJECTS

Introduction

This evidence-based guide has been developed from a systematic literature review and extensive primary research. It is designed to help you reflect on your ideas and goals for a **technology-supported change project** in health or social care and work towards a project plan. A high proportion of such projects fail, but there are ways of improving the chances that your project will succeed.

Technology projects are characterised by **complexity** – i.e. they have multiple interacting components that cannot be tightly controlled. Complex projects are unpredictable and risky, hence less likely to succeed than simple ones. This guide will help you to identify the different areas of complexity (that is, the uncertainties, interdependencies and possible unintended consequences) in your project and think of ways to reduce or manage these (e.g. by making some aspects simpler or mitigating risks)

How to use this guide

We recommend that you start using this guide as early as possible and keep revisiting it as your project unfolds. It will only take you a few minutes to skim through it and gain an initial orientation, but working carefully through the detail of the guide will take much longer. There is no 'right' way to use the guide; it is intended to prompt conversations and help you bring together different areas of expertise (such as clinical, technical and business development). For example, you could assign different parts of the guide to different people to fill in in detail, then reconvene and compare your responses. You may wish to employ a facilitator to run a workshop with the project team.

Structure of this guide

PART 1 of this guide is divided into 6 domains, each in two parts:

- **A free-text box for you to present this domain in your own words**. This will help surface the issues, technologies, people and activities relevant to *your* project and how they seem to fit together. Make it flow like a story (i.e. write in sentences rather than using tables or bullet points), so as to capture the messiness (non-linearity) of the project. Telling a brief story will allow you to draw out the 'plot' of what's happened so far and identify interdependencies and tricky issues that may contribute to the project's success or failure (or something in between).
- **Some questions to help you estimate key areas of complexity** (most of which should have come up in your narrative). The more red boxes you tick, the more complex this domain is (though the boxes don't carry equal weight, so adding up the ticks won't give you a quantitative score). The top-level questions are quite broad,

but if a question is particularly relevant to your proposed project, you can 'drill down' with the more detailed questions. Ideally, you should be able to back up your answers with evidence, such as published figures or research, or data you have collected yourself (for example from interviews or focus groups). Some questions will not apply to your project, so tick 'not applicable' for these. If a question seems relevant but you're not sure how to answer it, tick 'don't know' – and perhaps discuss this one with colleagues later. Can you distinguish the things you don't *yet* know (but could find out) from the things that are unknowable (inherently uncertain), which you have to handle with creativity and judgement as the project unfolds?

Note: [1] No single individual will be able to answer all the questions but you should find that if you involve a range of people across your organisation, you will be able to address all the domains. For each domain, we've suggested who might be best placed to answer the questions. [2] The tick-box questions will give an artificially structured and linear perspective. Bear in mind that complex change is an inherently messy and unpredictable process, but the box-ticking may help you find a 'way in' to your narrative.

PART 2 is designed to help your team handle the different kinds of complexity in your project. It consists of prompts to help you plan and manage an implementation project and think about how to

- **Reduce complexity** where possible (e.g. by limiting the scope of the project)
- **Respond to complexity** where it can't be reduced (e.g. by bringing staff together to make sense of a situation, strengthening relationships, or collecting and analysing real-time data)

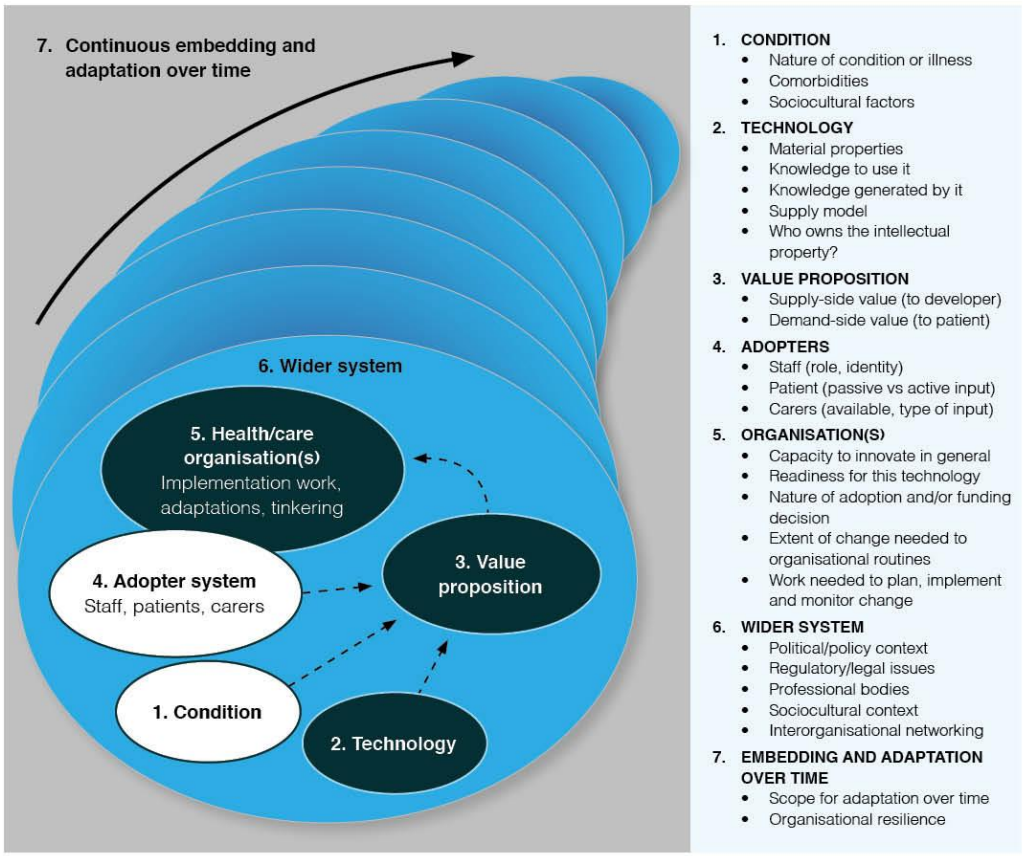


Diagram: The NASSS framework (© Greenhalgh at al J Med Internet Research 2017; 19 (11): e367)

➢ PART 1: ANALYSING COMPLEXITY IN YOUR PROJECT

➢ THE ILLNESS OR CONDITION

[a clinician, social worker or researcher might be the best person to complete this section]

Briefly describe the condition(s) for which the innovation or technology has been designed (e.g. heart failure, mental health, social isolation). In some situations, there won't be a specific illness or condition.

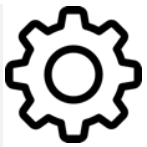
The following questions should help you summarise whether the condition or illness is straightforward, well-understood, follows a predictable course and has predictable implications for care. This isn't about whether the illness is serious*, but whether you can predict what will happen next. For suggestions for responding to complexity in this domain, see page 53.*

IDENTIFYING COMPLEXITIES IN THE ILLNESS OR CONDITION:	*Agree*	*Disagree*	*Not applicable or don't know*
There are significant uncertainties about the illness or condition *Additional detail – e.g.* ➢ *The condition is not clearly defined, or too little is known about it to inform planning* ➢ *The population affected by the condition is not well-defined* ➢ *The condition affects people in different ways, so a 'one size fits all' solution is unlikely to work* ➢ *People with the condition are likely to be under the care of multiple professionals and/or in more than one care pathway*			
Many people with the condition have other co-existing illnesses or impairments that could affect their ability to benefit from the technology or service *e.g.* ➢ *Physical or mental co-morbidities* ➢ *Cognitive impairment*			
Many people with the condition have social or cultural factors that could affect their ability to benefit from the technology or service. *e.g.* ➢ *Poverty* ➢ *Social exclusion e.g. drug use, homeless* ➢ *Religious restrictions or expectations on how they manage their illness* ➢ *Low health literacy (limited ability to understand health issues and how to handle them)* ➢ *Low system literacy (limited understanding of how services work and how to navigate them)* ➢ *Low digital literacy (limited ability to use, or learn to use, new IT products)* ➢ *Unable to understand the language used by professional staff*			

The population with the condition, and/or how the condition is treated, is likely to change significantly over the next 3-5 years			
SUMMARY: The illness or condition has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

- **THE TECHNOLOGY (or other innovation)**
  [the technology developer might be the best person to complete this section]

Describe the technology/ies or other innovation. It might be an app, a device, a tool, a protocol or pathway, an algorithm, a model, a piece of hardware – or some combination of these. Highlight what is new apart from the technology (e.g. new way of working).
An innovation can be old technology (e.g. telephone) used in a new way.



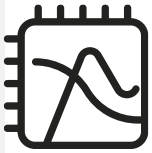
The questions below will help you decide if the technology (and how it works to support care) is straightforward, well-understood and will have a predictable effect. For suggestions for responding to complexity in this domain, see page 13.

IDENTIFYING COMPLEXITIES IN THE TECHNOLOGY OR OTHER INNOVATION:	*Agree*	*Disagree*	*Not applicable or don't know*
There are significant uncertainties about what the technology is *e.g.* ➢ *The technology is difficult to define (e.g. connects with hidden infrastructure, supplier does not disclose full details)* ➢ *The technology does not yet exist in a robust and definitive form*			
There are significant uncertainties about where the technology will come from *e.g.* ➢ *The technology supply chain is not yet in place* ➢ *The technology is not easily substitutable (i.e. if the supplier withdrew, it would not be obtainable elsewhere)*			
There are significant uncertainties about the technology's performance and dependability *e.g.* ➢ *Data collection and transmission (where relevant) are not yet accurate or reliable* ➢ *There are significant privacy or security concerns*			

There are significant uncertainties about the technology's usability and acceptability *e.g.* ➢ *It is not possible for people to try out the technology on a small scale before adopting it* ➢ *The data or knowledge generated by the technology is not well understood or trusted* ➢ *There is not yet evidence from prototyping that intended users find the technology easy to use without human support (e.g. clinician, carer or help desk)* ➢ *There is not yet evidence from prototyping that the technology is acceptable to its intended users (e.g. that it generates data that are well-understood and trusted, and which reflect how their condition is normally managed)*			
There are significant technical interdependencies *e.g.* ➢ *A key technology needs to be installed across multiple technical systems so as to achieve 'integration'* ➢ *The technology cannot be installed until the organisation's IT system is upgraded or changed (e.g. new hardware, better bandwidth)* ➢ *The technology would require individual users to upgrade their device(s) or home IT system* ➢ *The technology overlaps (unproductively) with an existing technology that performs the same or a similar function*			
The technology is likely to require major changes to organisational tasks and routines *e.g.* ➢ *Implementing the technology means some staff will have to do their jobs in a different way and/or interact with different people* ➢ *Implementing the technology will require new or different steps in the overall care pathway (e.g. new administrative processes)*			
The technology (and/or the service model it supports) is likely to change significantly within the next 3-5 years *e.g.* ➢ *The technology has limited potential to be adapted to take account of future clinical developments and other changes* ➢ *The technology supply model may not be sustainable (e.g. the client-supplier relationship is weak, or there are questions about the company's reputation)*			
SUMMARY: The technology has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

➢ THE VALUE PROPOSITION (costs and benefits of the technology) [the technology developer and business lead for the organisation might complete this section]

Describe the value (financial or otherwise) that the new technology and care model might generate. For commercial stakeholders, this may be return on investment. For patients, it may be cure, comfort, or quality of life. For healthcare organisations, it may be improvements in quality of care, efficiency (saving time, freeing up staff), safety (including reduced risk of litigation), or inclusivity.



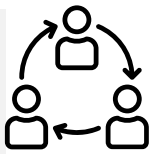
The following questions address what kind of value the technology might generate for different groups of people. For suggestions for responding to complexity in this domain, see page 14.

IDENTIFYING COMPLEXITIES IN THE VALUE PROPOSITION:	*Agree*	*Disagree*	*Not applicable or don't know*
The commercial value of the technology is uncertain *e.g.* ➢ *If the technology does not yet exist in a definitive form, the case for investing in its [further] technical development is weak* ➢ *The technology does not have a plausible business case, including up-front investment, a well-defined customer base and market drivers, consideration of competing products and realistic assessment of challenges of implementing at scale in a public-sector health or care environment*			
The value to the patient or client is uncertain *e.g.* ➢ *There are no high-quality studies (e.g. randomised controlled trials) to demonstrate the technology's efficacy for this patient/client group* ➢ *The technology's benefits have not been shown to outweigh its potential harms* ➢ *The technology's efficacy and safety were not measured in terms of an outcome that matters to patients*			
The value to the clinician or other staff member is uncertain *e.g.* ➢ *The technology may create work (or other hassles) for the front-line staff* ➢ *The technology's benefits have not been shown to outweigh the hassle of using it*			
The value to the healthcare system is uncertain *e.g.* ➢ *The technology (or the technology-supported care model) is not considered to have any overall advantage over existing practice* ➢ *The technology has not yet been shown to be effective and cost-effective in terms of how much benefit it will bring for a given financial outlay* ➢ *There are safety concerns about the technology or care model* ➢ *This technology-supported care model has not yet been successfully implemented in a similar context to the one being contemplated* ➢ *There are concerns that the technology, whilst improving care for some patients, could widen inequalities* ➢ *Regulatory and other approvals for the technology are not yet in place*			
The value to this particular healthcare organisation is uncertain *e.g.* ➢ *The technology will require new technical infrastructure before it can be introduced to this organisation (see Technology domain)* ➢ *The technology will require extensive changes to organisational routines and pathways (see Technology and Organisation domains)* ➢ *Aspects of the local procurement processes make it hard to commission this technology (see Organisation domain)*			
The technology could generate a negative value (i.e. costs are likely to outweigh benefits) for some stakeholders. *e.g.* ➢ *Potential loss of income* ➢ *Destabilising a provider* ➢ *Hidden or knock-on costs*			
The value proposition is likely to change significantly over the next 3-5 years. *e.g.*			

➢ *A new, better technology is on the horizon* ➢ *The market for the technology will change significantly* *A key regulatory decision could be made or reversed)*			
SUMMARY: The value proposition has significant complexity which is likely to affect the project's success	*Yes* ☐	*No* ☐	

➢ THE INTENDED ADOPTERS OF THE INNOVATION/TECHNOLOGY [this section should be completed by, or on behalf of, everyone who might use the technology]

Describe the intended users of the technology or other innovation. Consider: patients/lay people, professionals, administrative and support staff. Are there people who will be impacted indirectly (e.g. clinicians may be the main users but admin staff may need to adapt their procedures)?

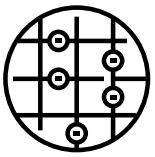


The following questions will help you summarise whether people directly involved with the technology understand what it is for, think it is worth trying, feel able to use it and are motivated to give it a go, and also what the indirect knock-ons may be for others. For suggestions for responding to complexity in this domain, see page 14.

IDENTIFYING COMPLEXITIES IN THE INTENDED ADOPTERS:	*Agree*	*Disagree*	*Not applicable or don't know*
There is uncertainty about whether and how patients/carers or citizens will adopt the technology *e.g.* ➢ *The technology would require substantial input from the patient or their immediate carer* ➢ *Some patients will view the technology in a negative way (e.g. not appropriate for their home, or reminding them of an illness they'd prefer to forget about)* ➢ *Quite a few people in the intended user group may be unable or unwilling to learn to use the technology*			
There is uncertainty about whether and how front-line staff will adopt the technology *e.g.* ➢ *Some staff members question the value proposition for the technology (e.g. they feel that adopting it would jeopardise the quality or safety of patient care, or they believe it is more time-consuming than existing practice)* ➢ *The technology would require staff to do their jobs differently, and perhaps take on a new, unwanted, role and identity (e.g. 'data entry person')* ➢ *Some individuals or teams do not have the resources, time, space or support to learn to use the technology* ➢ *Staff have not been trained or supported to be creative and flexible when implementing technologies*			
There is uncertainty about the implications for people who might be indirectly affected by the technology *e.g.*			

➢ *The technology would require input from others (e.g. relatives, care home staff), who may be unable or unwilling to learn to use it* ➢ *The technology would make someone else's job obsolete or more difficult*			
There will be significant changes to individual users' perceptions of the technology over the next 3-5 years *e.g.* ➢ *Key staff groups are likely to change their views on the technology* ➢ *Patients or their lay carers are likely to change their views on the technology*			
SUMMARY: There is significant complexity relating to the intended adopters which is likely to affect the project's success	*Yes* ☐	*No* ☐	

➢ THE ORGANISATION(S) IMPLEMENTING THE TECHNOLOGY [this section is best completed by people who know the organisation and the challenges it faces e.g. board member, human resources lead, staff representative]



Briefly describe the organisation(s) involved in the project (for example, digital agency, healthcare provider, social care provider). What kind of organisation is it? How is it structured – and what is it like to work there? What is its track record of taking up new technologies? How well-resourced is it (in terms of both staff and funding)? Is there much enthusiasm for this particular technology?
You may need to complete this section separately for the main and partner/ impacted organisations (and use the highest complexity score in your planning, since the initiative will only be as strong as its weakest link).

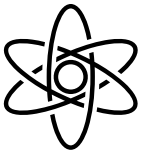
The following questions will help you assess whether the organisation is capable and ready to take on the innovation, and whether the work involved has been understood and planned for. For suggestions for responding to complexity in this domain, see page 15.

IDENTIFYING COMPLEXITIES IN THE ORGANISATION(S):	*Agree*	*Disagree*	*Not applicable or don't know*
The organisation's capacity to take on technological innovations is limited *e.g.* ➢ *Leadership is weak and the organisation's mission and values are unclear* ➢ *Internal relations, especially between managers and clinicians, are poor*			

➢ *The structure is top-down and hierarchical, so individual departments are discouraged from horizon-scanning for new products and ideas, and have limited scope to introduce innovations* ➢ *The organisation has a poor track record of introducing any kind of change* ➢ *There are no slack resources (people or money) to channel into innovative projects* ➢ *It is not a learning organisation: staff are not encouraged to meet and talk about new ideas and projects, there are few or no measures in place to capture data and monitor progress, and risk-taking is discouraged* ➢ *Digital maturity is low*			
The organisation is not ready for this particular innovation *e.g.* ➢ *The fit between the organisation's mission and the innovation is poor* ➢ *Key people (especially senior management) oppose the innovation or are unconvinced of its value* ➢ *The business case is weak or questioned (see Value Proposition domain)* ➢ *The implications (e.g. work required) of introducing, implementing and evaluating the technology have not been adequately assessed (or have been questioned)* ➢ *Money is needed but a budget line has not been allocated*			
Organisational routines and processes will need to change very considerably to accommodate the technology *e.g.* ➢ *Different kinds of staff (e.g. new hires) will need to be involved in the process or pathway once the technology has been introduced* ➢ *A new (or radically revised) process or pathway will need to be developed* ➢ *The core process or pathway will need to link differently with other key processes and pathways in the organisation*			
Procurement processes are in place that make it harder to commission this technology *e.g.* ➢ *The provider is not on the procurement framework* ➢ *Existing contracts need to expire first* ➢ *Aspects of the procurement process are not yet clear (e.g. Who will fund this? Who will be liable for costs? Is there an identified budget? It is capital or revenue ? Is the funding recurrent? Are there issues with timing/accruals of funding?)*			
The work needed to introduce and routinise the innovation has been underestimated and/or inadequately resourced *e.g.* ➢ *Work to bring people on board and develop a shared, organisation-wide vision for the change* ➢ *Work to develop, implement and mainstream new care pathways and processes* ➢ *Work to coordinate the project across more than one organisation or sector* ➢ *Work to evaluate and monitor the change*			
The organisation(s) involved are likely to have significant restructurings or changes in leadership, mission or strategy over the next 3-5 years			
SUMMARY: There is significant complexity relating to one or more participating organisations which is likely to affect the project's success	*Yes* ☐	*No* ☐	

➢ THE EXTERNAL CONTEXT FOR INNOVATION
[this section might be completed by a 'horizon-scanner' who looks beyond the organisation]

Describe the national and local context for your technology or programme (e.g. legal obligations, policy, professional bodies views on best practice, related national initiatives). Think about the key influences on the project beyond the organisation(s) you identified in the previous section.



The following questions will help you summarise whether there are external conditions (such as the state of policy, public/ professional opinion, expected external events such as political climate change) likely to complicate the adoption and mainstreaming of the innovation. For suggestions for responding to complexity in this domain, see page 17.

IDENTIFYING COMPLEXITIES IN THE EXTERNAL CONTEXT:	*Agree*	*Disagree*	*Not applicable or don't know*
The political and/or policy climate is adverse *e.g.* ➢ *External political or economic changes impacting on the organisation could threaten the introduction of the innovation* ➢ *Current policy priorities conflict with this initiative*			
Professional organisations are opposed to the innovation or don't actively support it *e.g.* ➢ *There are concerns about quality or safety of care* ➢ *There are concerns about confidentiality and wider information governance* ➢ *There are concerns about professional workload* ➢ *Priorities are elsewhere*			
Patient organisations and lobbying groups are opposed to the innovation or don't actively support it *e.g.* ➢ *There are concerns about quality or safety of care* ➢ *There are concerns about privacy and/or what will happen to the data* ➢ *Priorities are elsewhere*			
The regulatory context is adverse *e.g.* ➢ *Quality standards and regulatory requirements for using the technology in a health or care setting have not been fully defined* ➢ *Key stakeholders do not know about or accept these standards and requirements*			
The commercial context is adverse *e.g.* ➢ *The technology industry views the innovation (or similar products) negatively* ➢ *The technology does not use industry-standard components* ➢ *There is lack of support for timely updates to the technology to support ongoing work as intended*			
Opportunities for learning from other (similar) organisations are limited *Additional detail* ➢ *No other similar organisations are yet using the technology* ➢ *Inter-organisational knowledge exchange networks are weak*			
Introduction of the technology/innovation could be threatened by external changes that impact on the organisation			
The policy, regulatory and economic context for this innovation is likely to be turbulent over the next 3-5 years *e.g.* ➢ *Change of government*			

➢ *New policy priorities* ➢ *Economic recession* ➢ *New regulatory framework* ➢ *Withdrawal of industry commitment*			
SUMMARY: There is significant complexity relating to the external context which is likely to affect the project's success	*Yes* ☐	*No* ☐	

➢ EMERGENCE OVER TIME

[this section pulls together the bottom row of each of the previous domains]

Summarise the main changes which, if they happen, could affect the project over the next 3-5 years. Which of these do you think is most significant? What are the key uncertainties?

For suggestions for responding to complexity in this domain, see page 18.

ESTIMATING WHAT THE FUTURE HOLDS:	*Agree*	*Disagree*	*Not applicable or don't know*
The population with the condition, and/or how the condition is treated, is likely to change significantly over the next 3-5 years			
The technology (and/or the service model it supports) is likely to change significantly over the next 3-5 years			
The value proposition for the technology is likely to change significantly over the next 3-5 years			
There will be significant changes to individual users' perceptions of the technology over the next 3-5 years			
The organisation(s) involved are likely to have significant restructurings or changes in leadership, mission or strategy over the next 3-5 years.			
The policy, regulatory and economic context for this innovation is likely to be turbulent over the next 3-5 years			

➢ PART 2: ACTION PLANNING AND PROJECT MAGAGEMENT

Taking account all your responses to Part 1, this section prompts you and your team to **plan your implementation project** and consider measures to **reduce or respond to complexity** in the different NASSS domains. Below, we offer some ideas and resources to get you started. The resources and links have been selected for a UK setting but could easily be adapted for other countries.

Planning your implementation project

Skim this section first – but then go on to look at the different complexities and ideas for responding to them. You may end up deciding not to go ahead with the project at all.

Project management in a highly predictable environment is fairly straightforward, but under conditions of complexity, things can't be fully predicted or laid out in advance. You need to set a broad goal, take action on several fronts simultaneously (making sure you attend to the human and political aspects of the project as well as the technical and financial aspects), while periodically reviewing progress and adjusting your strategy.

For large, ambitious projects, we recommend the Project Initiation Routemap, a guide by the UK government for planning complex projects in the public sector. The Routemap emphasises three linked strategic tasks:

- Assess the complexity and context of the delivery environment (see NASSS questions above, especially Domain 2 'The Technology' and Domain 5 'The Organisation'), and consider how you could respond to this complexity (see suggestions below);
- Assess the capacity and capability of organisations and teams to deliver the project (in particular, sponsor, senior management buy-in and support, dedicated delivery team);
- Work to strengthen and align context and capability (e.g. align requirements, governance, execution strategy, organisation design and development, procurement, risk management, asset management).

See also the NESTA DIY toolkit for bringing ideas to life (designed for social care providers) – a structured way to get from the initial idea for a new technology to a well-designed project to get it up and running in a service.

Due diligence. Before investing in a technology, make sure the company selling it is legal and solvent, that the technology has the requisite regulatory approvals, that personal data is handled sensitively and respectfully, and that any associated risks have been considered. There are numerous due diligence checklists available – see these for example:

UK government digital service standards – a 14-point checklist when planning a service that involves digital technology. Linked to these are UK government technology and digital standards.

How to do due diligence for health care technologies – introductory blog from private company SecureDocs.

Digital Assessment Questionnaire from NHS Digital, a self-assessment checklist for apps and similar technologies.

Medical devices – software applications – Advice from the UK government on when software applications are considered to be a medical device and how they are regulated.

NHS Health and Social Care Data Security Standards (including a full due diligence checklist for suppliers).

UK government code of conduct for data-driven health and care technology – Principles and advice for machine learning applications that use NHS data.

Commercialising new technologies. If you are developing a new technology and you think it has commercial potential, you will need to systematically demonstrate to investors how it will generate value. Try this resource:

Guidance and Impact tracking System (GAITS) – a web-based project and portfolio management platform designed to support commercialisation of new health technologies, developed by the US consultancy firm CIMIT.

Adoption Readiness Level tool by Liverpool City Region's e-health cluster – a self-assessment tool for tech developers that considers five domains (market, human, systems integration, finance/procurement, motivation).

Responding to complexity in the illness or condition

Your first step in developing technological solutions for an illness or condition is to understand the full range and depth of what the illness *is* and how it affects people.

Find out more about the illness. For example, find the prevalence, likely progression, and current 'best practice' care model. This will allow you to estimate how many users a product is likely to have, how long they can/will use it for, and how this fits with current care. Remember, there will be 'mild' and 'severe' forms of the illness, different age groups, ethnicities, genders and so on. Once you understand how the illness is patterned, this could inform work to 'personalise' the technology for different sub-groups (see 'Responding to complexity in the intended users' below). To learn about the illness, use different data sources, e.g. from national and regional databases, academic and grey literature, health and care practitioners, patient organisations, patients. For example:

NHS Choices – a searchable database of illnesses, including diagnosis, treatment and likely course

NICE guidelines - evidence-based recommendations in a variety of conditions, procedures and technologies across health and social care developed by independent committees

Cochrane library – a database of high-quality systematic reviews of treatments

Healthtalk – a database of patients' accounts of what it's like to live with different illnesses

Macmillan – a website for people with cancer, with detailed information on prevalence, treatment and prognosis. There are similar patient-facing websites for most conditions. Explore them!

Responding to complexity in the technology(ies)

Don't make the mistake of treating a new technology as a plug-and-play solution. You need to ask a lot of questions about it before you can be sure it's the right tool for the job. New technologies often look appealing and promising until we consider all aspects of the innovation process.

Find out more about the technology and assess its quality and implications. If you are not the creator of the technology, familiarise yourself with all relevant aspects of it or ask an expert. Look at it; play with it; do a 'walk through' the imagined use case. Will this product really help with what you are planning to achieve? Could a different technology (perhaps one that is already tried and tested) do a similar job with less hassle?

NHS apps library – a searchable database of quality-assured smartphone health apps

Publicly available 'curated' databases of apps – for example:

- Psyberguide for mental health apps
- ORCHA, an independent organisation that evaluates apps

Find out more about where the technology will come from and associated challenges. Ideally the building blocks for your chosen technology e.g. coding platform, devices etc can be accessed or purchased easily (no long waiting periods or unreliable supply chains). Ideally, the technology should not depend on a single vendor/device/coding language etc, but work (or have the potential to work with or easily change to) others as well. They will have been tested extensively so you don't have to worry about these components being dependable. Conflicts of interest and claims to intellectual property (IP) should be sorted out before the project begins. It should be clear who will fund the technology, what it will cost and which costs are covered (set up, maintenance, updates etc).

Identify and address the key points where technical complexity will impact on success. Find out about any unknowns and dependencies as soon as possible, and develop a plan to deal with them, including alternatives or workarounds. Reduce unnecessary technical integration. Integration between multiple systems makes everything more complex. Ask whether it is really necessary or if there are ways to avoid or delay this, especially during initial testing. But bear in mind that some forms of technical integration (e.g. to make a new piece of software accessible from within a patient's existing electronic record) may make the technology *simpler* for a clinician to use.

Consider how the technology will disrupt the system. Map possible disruptions and take steps to avoid or mitigate them. Can you modify the technology to make it less disruptive? Can you reduce knock-ons by adjusting other systems or processes? What measures might you put in place (e.g. small-scale pilot running in parallel with the old service, on-the-job training, help desk) to deal with the disruption until systems and processes have evolved to accommodate the new technology? We pick up this important point again under 'the organisation' below.

Responding to complexity in the value proposition

This project is only going to work if all stakeholders gain something of value from it.

Consider how to increase the technology's appeal to investors. If the technology is at an early stage of development, what is its likely upstream value as viewed by investors (especially the business case for generating profits, further spin-offs, and highly qualified jobs), drug and device regulators (preliminary evidence of efficacy and safety), and financial regulators (auditable business processes and governance)? Can the technology be 'de-risked' by removing costly but inessential features? See the Guidance and Impact tracking System (GAITS) resource linked above.

Consider how to increase the technology's value to patients or citizens. If a technology is meant to be used by patients or lay people, its potential benefits must be weighed against its costs (and the person's willingness and ability to contribute to these), the work needed to use it (and whether the person or their carer is able and willing to do that work), and the desirability of medicalisation and surveillance. Can the design be improved to make the technology more appealing? Can the data be visualised in a way patients or carers can engage with?

> See links above under 'Responding to complexity in the illness'
>
> Getting the most out of PROMS – A guide to using patient-reported outcome measures to assess whether an intervention or technology is actually improving outcomes that are valued by patients
>
> A guide to PROMs methodology from NHS Digital (using hip and knee replacement as an example)

Identify evidence of effectiveness and cost-effectiveness. If the technology is at a more advanced stage of development, there may be research evidence comparing its effectiveness (does it work?) and cost-

effectiveness (is it good value for money?) with 'usual care' and measuring an outcome that is important to patients. Try these resources:

> NICE Evidence Standards for digital health technologies – These cover both effectiveness and economic impact.

Consider real-world value issues. Is there a realistic assessment of the challenges of implementing this innovation at scale in a particular public-sector health or care environment? Even when something has been shown to be cost-effective, it may not be locally affordable or a funding priority.

> The NICE Evidence Standards website linked above offers a budget impact guide and budget impact template for local cost planning.

Responding to complexity in the intended adopters of the technology

This project is only going to work if the people you want to use the technology are able and willing to do so.

Address acceptability, accessibility and usability for patients and citizens. If the technology requires input from a patient, carer or other lay person, will they find the product aesthetically pleasing and easy to use? Does the technology make sense, for example, in the context of how patients and carers already do things, their routines and existing tools they use to support their work? Remember, everyone is different. Some people have limited vision or dexterity; some people find instructions hard to understand. Can you make the product more accessible? Is it worth building design changes in now or planning to do so in the future (e.g. after proof of concept testing)? If the technology includes several components, can users select what is most relevant for them? These resources may help:

> How to do research on user needs in the 'discovery phase' of technology design – a website from the UK government.
>
> International Design Foundation – a US site offering tips and resources for making websites and apps more accessible.
>
> How to design websites for older people – a guide from the Alzheimers Society.

Address staff motivation and concerns. Assess the level of enthusiasm for the technology from different staff groups, and also how motivated teams are to take on the new technology. Have any of them had experience of using this technology elsewhere? Listen to staff concerns – which may be legitimate – and to their ideas for increasing the project's success. This resource may help:

> Higher Education England Digital Capabilities Framework for assessing the digital capability of staff.

Modify staff roles and provide training. Develop new roles and job descriptions where needed, perhaps by adapting ones already in use elsewhere. Set learning objectives (some of which will be about building confidence to make judgements, not about mechanically following protocol). Design and develop training courses. Remember: using a technology usually needs on-the-job and team-based training, not just sitting in classrooms. Allocate sufficient budget for this work, and consider issues such as backfill.

Promote social learning. One way to become confident in using a technology is to shadow someone in the same role who is already an enthusiast for it ('champion') and confident in using it ('super user'). Learning in this way not only develops skills but also helps people develop a positive attitude and identity.

Support collective sensemaking and communities of practice. People need to make sense of new technologies – sometimes by coming together to complain about them initially! Surfacing one's irritation with a technology may be the first step to coming to terms with it. Both staff and patients may benefit from being in 'communities of practice' (groups or networks of people who share an interest in something and are trying to

get better at it). Online communities of patients, for example, are often good sources of knowledge and wisdom about how to manage a condition. Try to get these communities on board if introducing a patient-facing technology.

The Kings Fund guide to engaging NHS staff may provide some practical ways of achieving the above.

Responding to complexity in the organisation

The project is only going to work if the organisation has the capacity to take on innovations and if there is good 'innovation-system fit'. The tips below may help if you are trying to support an organisation to implement a new, technology-supported care model.

Assess the organisation's capacity to innovate. An innovative organisation has strong leadership, good clinician-managerial relations, a devolved management structure, slack resources (money and/or staff) that can be channelled into new projects, good lines of communication and an ethos where it's OK to take risks and learn from failures. If an organisation appears to lack these essential prerequisites for innovation, consider whether you need to strengthen its capacity before pressing ahead. Here are some questions to help you assess capacity to innovate:

- Is there a culture that supports innovation and change (e.g. are staff trusted to introduce new ideas)?
- Does the organization have systems and processes in place that support innovation and change e.g. effective information and communication systems, opportunities for networking and learning across departments/teams?
- Do the senior management team actively seek opportunities for improvement and encourage ideas and feedback from patients, the public and staff?
- Are the organisation's leaders helping to create a facilitative context through providing motivation and support, creating a vision and reinforcing the change process?
- Is there a distributed and devolved style of management?
- Is there a history of introducing successful change in comparable projects at a local level?
- Are there mechanisms in place to support learning and evaluation and to embed changes in routine practice e.g. regular team meetings, audit and feedback processes, professional development opportunities and performance review systems?

Assess innovation-system fit. Even when an organisation is capable of running a successful project to implement a new technology, it might be the wrong technology to introduce in this organisation right now. Has the organisation successfully adopted similar technologies in the past? Are its strategic priorities aligned with the use of the proposed technology? Or are other projects more pressing?

Assess the implications of the technology for the organisation. Careful mapping out of tasks and processes is necessary to surface how the technology or other innovation is likely to change these. The pathway in which the technology is used directly (e.g. clinical care) may have indirect knock-ons for other processes and pathways (e.g. booking, correspondence, billing). You need to estimate costs (both initial and recurrent), and consider how money will need to flow across the system. Before signing off on a project, boards generally want to know how much will it cost up-front, what the likely savings will be, and when these savings will occur. These resources may help:

Process mapping guide from NHS Improvement. Ideas and tools for mapping the steps in a care pathway. A full list of additional service improvement and redesign tools from NHS Improvement is available here.

Using costing information to support better outcomes – a guide from NHS Improvement.

Assess the level of 'political' backing for the innovation. For an organisational-level adoption decision to be approved, it needs support from both top management (a 'senior sponsor') and the rank-and-

file. Supporters of the change must outnumber opponents and be more strategically placed. People with 'wrecking power' can block progress and may need to be brought on board (or worked around). To assess all this, use the NASSS-CAT PROJECT tool and also:

> Stakeholder analysis guide from NHS Improvement. This guide will help you construct a table or chart listing all the stakeholders who will need to accept (and, in many cases, start to use) the technology. Consider each key stakeholder's perspective (and their potential wrecking power).

Consider inter-organisational relationships. Costs and benefits of technology projects are hard to predict, and savings may accrue elsewhere in the system. When there is no pre-existing contractual relationship between organisations, it can be hard to reach a satisfactory arrangement for how to manage these uncertainties.

Think how (and by whom) success will be evaluated. If this project is going to happen, you will need to monitor how well the change is going. You will almost certainly need both quantitative metrics (to answer the "how many…?" and "are we on track…?" questions) and also qualitative measures (to answer the "how do people feel about this…?" questions). Evaluation is everyone's job, and data are often best collected by people doing the job. Extensive data collection can be time-consuming and slow the project down (i.e. the perfect may be the enemy of the good).

> Evaluation: what to consider – A guide by the Health Foundation. This basic guide includes qualitative and quantitative approaches.
>
> The 'rainbow framework' for evaluation and monitoring by Michael Quinn Patton. It takes you through 7 colour-coded steps, namely Manage (e.g. define stakeholders, secure funding), Define (set a scope for the evaluation), Frame (intended users of the evaluation, what they will use it for, what success will look like), Describe (sample, measures/metrics, data sources, analytic approaches), Understand Causes (deeper analysis to produce explanatory models), Synthesise (combining results), and Report & Support Use (publishing and disseminating).
>
> Evaluation Works and Evidence Works toolkits to guide commissioning decisions, produced by West of England Academic Health Sciences Network and their partners.

Allocate funding. Studies of 'failed' technology projects often identify inadequate funding as a leading cause. You will probably need substantial set-up funding and possibly a recurrent budget line (for things like licences and IT support). Budget adequately for staff to learn and adjust as the transition occurs (see 'Responding to complexity in the intended adopters' above).

Manage the transition. Good change management involves a combination of 'hard' and 'soft' approaches. As well as setting goals and milestones and using agreed metrics to monitor progress, you also need to create opportunities for staff to come together and talk about the technology and new care model. As noted above, collective sensemaking, training (especially on-the-job training for both individuals and teams) and social learning from champions and super-users is crucial for building capacity. Use creative tools such as flip-charts and post-it exercises to surface people's interpretations and concerns. Invite them to come up with creative ideas and solutions to any problems they identify. Allocate sufficient budget for this work, and consider issues such as backfill. This guide may help:

> Leading large-scale change: a practical guide from NHS England.

Responding to complexity in the external environment

Plans for technology-supported change locally are unlikely to work out if there is a major mis-match with national policy or the prevailing political, economic or professional environment.

Try to align your project with current policy priorities. If the technology is actively supported in policy, it will be easier to introduce. If priorities are elsewhere, it may be worth trying to 'rebrand' the work to fit these.

Address regulatory issues and challenges. Consider which regulations (from which regulatory bodies) are relevant to the introduction of this technology. Are all approvals already in place? If not, who do you need to work with to make progress in this regard? See 'Due diligence' section on page 52.

Get the professions on board. If clinicians or social workers believe that the technology compromises the care of their patients or clients, or if they view it as demeaning to their role or a threat to their professional jurisdiction or income, their professional bodies may oppose it. Early dialogue with such bodies may avert such a situation.

Establish inter-organisational networks or collaboratives. Complex, organisation-wide change is a lot easier if change agents in one organisation can network with their opposite numbers in comparable organisations – for example in quality improvement collaboratives or learning sets. Here's a resource for that:

Improvement collaboratives in health care – A guide from the Health Foundation.

Keep a close eye on the outer context. External shocks to an organisation (such as economic turbulence) make change precarious. Whist such shocks are often hard to predict, it is a good idea to see what's on the horizon. The following questions may help you:

- Does the new technology and the proposed changes to services align with the strategic priorities for the wider health system e.g. in terms of current health policy, national priorities for action and improvement?
- Are there incentives in the wider health system that reinforce the proposed change e.g. pay for performance schemes, regulatory requirements etc.?
- Are there existing inter-organisational networks (e.g. specialised clinical networks) that will be helpful in terms of supporting the proposed changes?
- How much stability/instability is there in the wider health system – and how might this likely influence the implementation project?

Responding to emergent complexity (new complexities that develop over time)

The point about emergent change is it's difficult if not impossible to predict. So this domain is really about how you might build resilience in your staff and your organisation to enable them to respond to things that come up in the future.

Acknowledge unpredictability. Have you left open the possibility that the project might unfold in one of several different ways? Can you flesh out these different possible futures and talk them through with your stakeholders?

Recognise and support self-organisation. Front-line teams will 'tinker' – that is, try to adapt the technology and the work process to make them work better locally. Are you able to capture data to evaluate and support these efforts?

Facilitate interdependencies. Have you identified the key interdependencies in the project? Is there anything you can do to strengthen existing interdependencies or develop and strengthen new ones?

Maintain space for experimentation and sensemaking. As complex projects unfold, staff will need to tinker more, and also talk about what's happening. Encourage them to admit ignorance, explore paradoxes, exchange different viewpoints (there's no need for them to agree on a single version of the 'truth'!) and reflect collectively.

Develop adaptive capability in staff and teams. Train your staff to be creative and to adapt to change as it happens. They will sometimes need to make judgements in the light of incomplete or ambiguous data.

Attend to human relationships. Dealing with emergent problems requires give-and-take. It's sometimes a matter of muddling through. This will happen more easily if people know, like and trust each other.

Harness conflict productively. There is rarely a single, right way of addressing a complex problem, so view conflicting perspectives as the raw ingredients for producing multifaceted solutions.

NASSS-CAT (INTERVIEW VERSION)

RESEARCHING IMPLEMENTATION OF TECHNOLOGY PROJECTS

Introduction

This set of prompts for semi-structured interviews covers the different domains in the NASSS framework shown below. It will need to be adapted to suit the particular project that you are researching.

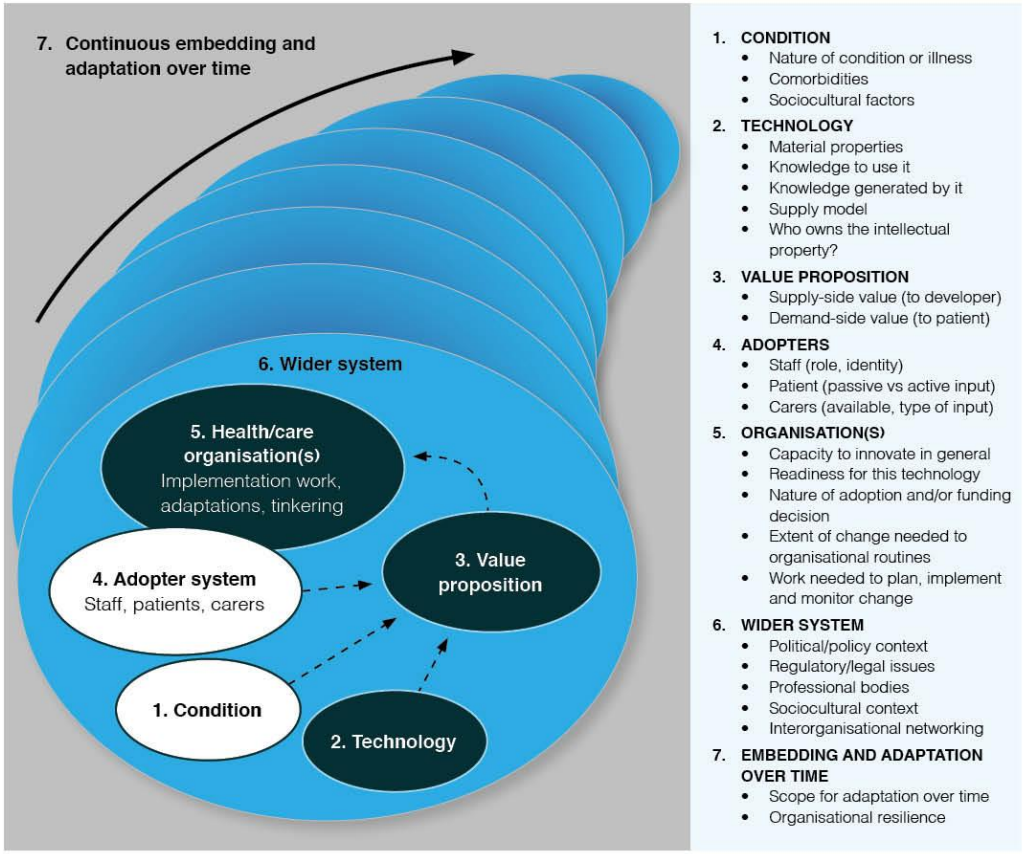


Diagram: The NASSS framework (© Greenhalgh at al J Med Internet Research 2017; 19 (11): e367)

- THE CONDITION OR ILLNESS

Ask these questions of a clinician, social worker or someone else who understands the underlying illness or condition for which the technology was designed

1. Tell me about the illness or condition for which this technology was [is being] designed.

   Prompts:
   - *Is the condition well-defined? How much is known about it?*
   - *Do you know how many people are be affected by the condition, and in what way?*
   - *Does the condition affect people in different ways? If so, can you give examples?*
   - *Would people with the condition need input from more than one specialist or be in more than one care pathway?*

2. Do people with the condition tend to have other illnesses or factors that need to be taken into account when designing the technology?

   Prompts:
   - *Are there physical co-morbidities (e.g. does it affect the very old or those with a pre-existing condition)?*
   - *Do some of the people affected have cognitive impairment, learning difficulties or communication difficulties?*
   - *Do people with the condition tend to be in multiple care pathways or see more than one provider?*

3. Do the target population for this technology have social or cultural factors that need to be taken into account when designing the technology?

   Prompts:
   - *Are some of them likely to be socio-economically disadvantaged, homeless or socially excluded?*
   - *Might some have religious restrictions or expectations that would affect how they manage their condition and their acceptance of technologies?*
   - *Are some likely to have low health literacy (poor understanding of what is wrong and how to manage it)?*
   - *Are some likely to have low system literacy (poor understanding of how to navigate the health or care system)?*
   - *Are some likely to have low digital literacy (poor understanding of technologies and how to use them)?*
   - *Are some of them likely to have problems understanding the language used by staff?*

4. How do you think the condition and the population it affects might change over the next 3-5 years?

   Prompts:
   - *Is the prevalence likely to increase or decrease?*

- THE TECHNOLOGY (or other innovation)

Ask these questions of the technology developer or someone else who knows the design aspects and technological detail.

1. What exactly is the technology?

   Prompts:
   - *Does it exist yet? If not, how much uncertainty is there around what it will be like?*
   - *Is the technology easy to define – or are there some vague elements e.g. connects with hidden infrastructure, supplier does not disclose full details?*
   - *Is the current version of the technology the definitive version?*

2. Where will the technology come from?

   Prompts:
   - *Has a supplier been identified?*
   - *Is the supply chain in place?*
   - *Is the technology easily substitutable (e.g. if the supplier withdrew, would it be possible to get this or a similar technology from elsewhere)?*

3. How would you rate the technology's performance and dependability?

   Prompts:
   - *Does it capture, and where appropriate transmit, data accurately and reliably?*
   - *Are there any privacy or security concerns?*

4. To what extent do you think the technology is usable by, and acceptable to, its intended users?

   Prompts:
   - *Can people try it out before committing to it?*
   - *Do they understand what it does and the data it generates?*
   - *What are the challenges of actually using it in practice?*
   - *Have you observed people trying to use it? What do they say?*
   - *What help do you offer users (e.g. helpdesk, hands-on support)? What has been the experience of supporting the introduction of the technology?*

5. Are there any key technical interdependencies?

   Prompts:
   - *Are there plans to make the technology connect with existing infrastructure?*
   - *Does it need to be installed across multiple technical systems to achieve 'integration'?*
   - *Will there need to be an upgrade to the organisation's IT system (e.g. new hardware, better bandwidth) to support use of the technology across the organisation?*
   - *Would any target users have to upgrade their personal device(s) or home IT system?*

6. To what extent do you think this technology implies major changes to the way healthcare is delivered?

   Prompts:
   - *To what extent would implementing the technology require staff to do their jobs in a different way and/or interact with different people or teams?*
   - *To what extent would implementing the technology require new or different steps in the care pathway (e.g. new administrative processes)?*

7. To what extent do you think the technology (and/or the service model it supports) will become obsolete or require updating in the next 3-5 years?

   Prompts:
   - *To what extent can the technology be adapted to take account of future changes?*
   - *To what extent will the technology supply model change?*

- **THE VALUE PROPOSITION (costs and benefits of the technology)**

Ask these questions of the technology developer or business lead for the organisation.

1. What is the commercial value of the technology?

   Prompts:
   - *If the technology does not yet exist in a definitive form, how strong is the case for investing in its [further] technical development?*
   - *Is there a plausible business case for developing the technology (including up-front investment, a well-defined customer base and market drivers, consideration of competing products and realistic assessment of challenges of implementing at scale in a public-sector health or care environment)?*

2. What is the value of the technology to the patient or client?

   Prompts:
   - *Are there any high-quality studies (e.g. randomised controlled trials) to demonstrate the technology's efficacy for this patient/client group?*
   - *What evidence is there that the technology's benefits outweigh its potential harms?*
   - *Have the technology's efficacy and safety been measured in terms of an outcome that matters to patients/clients?*

3. What is the value of the technology to the clinician or other professional?

   Prompts:
   - *Does the technology create work – if so, for whom?*
   - *Have the technology's benefits to the clinician been shown to outweigh the hassle of using it?*

4. What is known about the value that this technology could bring to the health or care system?

   Prompts:
   - *Has the technology (or the technology-supported care model) been shown to have an overall advantage over existing practice?*
   - *Has technology been shown to be effective and cost-effective in terms of how much benefit it will bring for a given financial outlay?*
   - *Are there any safety concerns about the technology or the care model it supports?*
   - *Has this technology-supported care model been successfully implemented in a similar context to the one being contemplated?*
   - *Are there concerns that the technology, whilst improving care for some patients, could widen inequalities?*
   - *Are regulatory and other approvals for the technology in place?*

5. What is known about the value that this technology is likely to being to this particular organisation?

   Prompts:
   - *Will new technical infrastructure be needed?*
   - *Will the organisation need to introduce substantial changes to organisational routines and pathways?*

6. Could the technology generate a negative value (i.e. costs would be more than gains) for some stakeholders?

   Prompts:
   - *Potential loss of income?*
   - *Destabilising a provider?*
   - *Hidden or knock-on costs?*

7. Is the value proposition likely to change over the next 3-5 years?

   Prompts:
   - *A new, better technology is on the horizon?*
   - *The market for the technology could change significantly?*
   - *A key regulatory decision could be made or reversed?*

- THE INTENDED ADOPTERS OF THE TECHNOLOGY

Ask these questions of anyone who uses, or is expected to use, the technology.

1. What do patients and carers think of the technology?

   Prompts:
   - *Does the technology require substantial input from the patient or their immediate carer?*
   - *What is the meaning of the technology to the patient? (Do they like using it? Do they mind having it in their home? Does it remind them of an illness they would rather forget about?)*
   - *What are the practicalities of using the technology? (Are they prepared to learn to use it? Can they make it work? If not, why not?)*

2. What do front-line staff think of the technology?

   Prompts:
   - *Do staff question the value proposition for the technology (e.g. do they feel that adopting it would jeopardise the quality or safety of patient care, or do they think it is more time-consuming than existing practice)?*
   - *Would the technology require staff to do their jobs differently and perhaps take on a new, unwanted, role and identity (e.g. 'data entry person')?*
   - *Do individuals or teams have the resources, time, space or support to learn to use the technology?*
   - *Are staff confident to be creative and flexible when implementing technologies, and is there organisational support for this adaptive approach?*

3. Are there people who are indirectly affected by the technology?

   Prompts:
   - *Would technology require input from others (e.g. relatives, care home staff), who may be unable or unwilling to learn to use it?*
   - *Would the technology would make someone else's job obsolete or more difficult?*

4. How do you anticipate that individual users' perceptions of the technology will change over the next 3-5 years?

   Prompts:
   - *Do you think patients or their lay carers are likely to change their views on the technology?*
   - *Do you think key staff groups are likely to change their views on the technology?*

- THE ORGANISATION(S)

Ask these questions of people who know the organisation and the challenges it faces e.g. board member, human resources lead, staff representative.

1. How would you rate the organisation's overall capacity to take on technological innovations?

   Prompts:
   - *How strong is the leadership?*
   - *Are the organisation's mission and values are clear?*
   - *How good are internal relations, especially between managers and clinicians?*
   - *Would you describe the management structure as flat and egalitarian or top-down and hierarchical? (For example, are individual departments discouraged from horizon-scanning for new products and ideas, and are they frowned upon if they introduce innovations?)*
   - *What is the organisation's track record of introducing any kind of change?*
   - *To what extent are there slack resources (people or money) to channel into innovative projects?*
   - *To what extent is it a learning organisation (in which staff are encouraged to meet and talk about new ideas and projects, there are measures in place to capture data and monitor progress, and risk-taking is encouraged?*
   - *What is the current level of digital maturity?*

2. To what extent do you think the organisation is ready for this particular technology/innovation?

   Prompts:
   - *Is there a good fit between the organisation's mission and the innovation?*
   - *Are there any key people (especially senior management) who oppose the innovation or are unconvinced of its value?*
   - *Is the business case strong and accepted?*
   - *Are the implications (e.g. work required) of introducing, implementing and evaluating the technology have been adequately and realistically assessed?*
   - *If money is needed, has a budget line been allocated?*

3. To what extent do you think organisational routines, pathways and processes will need to change to accommodate the technology/innovation?

   Prompts:
   - *Will different kinds of staff (e.g. new hires) need to be involved in the process or pathway once the technology has been introduced?*
   - *Will a new (or radically revised) process or pathway will need to be developed?*
   - *Will the core process or pathway need to link differently with other key processes and pathways in the organisation?*

4. Are there any relevant challenges in procurement processes that would make it harder for the organisation to invest in this technology?
   Prompts: For example…
   - *Is the provider on the organisation's procurement framework*
   - *Are there any existing contracts that need to expire first?*
   - *Are there aspects of the procurement process that are not yet clear (e.g. Who will fund this? Who will be liable for costs? Is there an identified budget? It is capital or revenue? Is the funding recurrent? Are there issues with timing/accruals of funding?)*

5. To what extent do you think the work of implementation has been realistically assessed and adequately resourced?

   Prompts:
   - *Work to bring people on board and develop a shared, organisation-wide vision for the change?*
   - *Work to develop, implement and mainstream new care pathways and processes?*
   - *Work to coordinate the project across more than one organisation or sector?*
   - *Work to evaluate and monitor the change?*

6. To what extent do you think the organisation(s) are likely to have significant restructurings or changes in leadership, mission or strategy over the next 3-5 years in a way that will impact on this project?

- THE EXTERNAL CONTEXT FOR INNOVATION

Ask these questions of people work outside the organisation or a 'horizon-scanner' who looks beyond the organisation.

1. What do you think of the political/policy climate as it relates to this innovation?

   Prompts:
   - *External political or economic changes impacting on the organisation which could threaten the introduction of the innovation?*
   - *Current policy priorities that conflict with this initiative?*

2. Do you think professional organisations support or oppose this innovation?

   Prompts:
   - *Concerns about quality or safety of care?*
   - *Concerns about confidentiality and wider information governance?*
   - *Concerns about professional workload?*
   - *Other pressing priorities?*

3. Do you think patient organisations and lobbying groups are likely to support or oppose this innovation?

   Prompts:
   - *Concerns about quality or safety of care?*
   - *Concerns about privacy and/or what will happen to the data*
   - *Other pressing priorities?*

4. Is the regulatory context supportive or adverse for this innovation?

   Prompts:
   - *Have quality standards and regulatory requirements for using the technology in a health or care setting been fully defined?*
   - *Do key stakeholders do not know about and accept these standards and requirements?*

5. Is the commercial context supportive or adverse for this innovation?

   Prompts:
   - *Does the technology industry view this innovation (or similar products) positively or negatively?*
   - *Does the technology use industry-standard components?*

6. Are there opportunities for learning from other organisations?

   Prompts:
   - *Is the innovation up and running elsewhere – or are others planning to implement it in a similar time frame?*
   - *Are there established inter-organisational knowledge exchange networks (e.g. quality improvement collaboratives) or could these be set up?*

7. Are there other external changes that could threaten introduction of the technology?

8. How do you think the policy, regulatory and economic context for this innovation is likely to change over the next 3-5 years? Is there likely to be turbulence?

   Prompts:
   - *Change of government?*
   - *New policy priorities?*
   - *Economic recession?*
   - *New regulatory framework?*
   - *Withdrawal of industry commitment?*