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IMPACT PROJECT

RECOVERING BREAST CANCER PATIENTS' VIEWS ABOUT THE USE OF IN-VIVO BIOSENSORS TO PERSONALISE RADIOTHERAPY TREATMENT

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Contents

Executive summary	3
1. Introduction	4
2. Methods.....	5
2.1 Sampling:.....	5
2.2 Recruitment	6
2.3 Research questions	7
2.4 Interview process	10
2.5 Data management, analysis and feedback	11
3. Results.....	12
3.1 Patient demographics and breast cancer experience	12
3.2 General views of biosensors	12
3.3 Risk, doubt and complications	13
3.4 Size and shape.....	14
3.5 Number of biosensors.....	15
3.6 Duration of biosensors in the body?	15
3.7 Power and data transmission options	16
3.8 Data security	17
4. Discussion and conclusion	17
Bibliography	20
Appendix 1: Potential uses of the biosensor in breast cancer treatment.....	24
Appendix 2: Participant information sheet and consent form	25
Appendix 3: Interview schedule	29

Executive summary

This report covers an important component of the EPSRC-funded IMPACT project that is developing implantable biosensors to monitor the tumour micro-environment so as to target X-ray dosage to hypoxic areas, thereby maximising the effectiveness of the treatment (www.eng.ed.ac.uk/impact).

This qualitative study explored the views of breast cancer patients about implanted biosensors through a series of semi-structured interviews with 32 women who had successfully completed a course of treatment. The aim was both to consider detailed aspects of patients' willingness to benefit from a possible technological enhancement of treatment and also to understand their views on the challenges of living with what that treatment might mean.

Interview questions covered the following aspects related to the development of the IMPACT device:

- Views (both positive and negative) regarding the use of implanted biosensors.
- The acceptability of different shapes, sizes and insertion techniques and the levels of discomfort they may cause.
- The length of time for which it is acceptable to retain the sensor (days, months, years).
- The risks attached to insertion and use of the biosensor.
- Views on the security of data transfer from the sensor to computers or databases, including storage, use, and access to data.

Nearly all of the patients expressed a willingness to have an implanted biosensor or biosensors for future cancer treatment. This was based on 1) trust in health professionals and 2) the context of having cancer. Willingness however was also matched in some cases with ambivalence relating to the evidence base for the technology, possible discomfort on insertion and dislike of wires penetrating the skin barrier. Most patients preferred a wireless power and data transmission option as this was perceived to be less intrusive on the body and easier to manage in the context of their everyday life. In terms of size and shape of biosensors, some patients expressed a preference for a smaller size, and smooth, long shape with rounded edges.

The views of cancer patients who have successfully completed their anticancer treatment are important as they may provide a guide to the acceptability of implantable diagnostic devices when used in groups of cancer patients in the future. The point of patient engagement, as in this project, is not to 'drive' the design process per se but to sensitise the designers to the preferences of the users. The results also demonstrate, to some extent, a prioritisation of the technological challenges as socially understood. This then is not only about patient willingness to benefit from a possible technological enhancement of treatment – to which the answer will only ever be positive – but to understand the challenges of living with what that treatment might mean.

1. Introduction

Breast cancer is the most common cancer in women in the UK (Kunkler 2003; Mistry *et al.* 2011). Every year approximately 50,000 women are diagnosed with breast cancer (Cancer Research UK 2013), and the annual incidence rate for breast cancer per 100,000 women has risen from 80 in 1985 to 157 in 2010 (Cancer Research UK 2012).

Radiotherapy is an important part of the multidisciplinary management of breast cancer. For every four first recurrences of breast cancer prevented by radiotherapy, one breast cancer death is avoided (Darby *et al.* 2011). Most radiotherapy is given after breast conserving surgery and selectively after mastectomy. Preoperative radiotherapy (Bondiau *et al.* 2013) is under investigation in combination with anti-cancer drug treatment to shrink larger primary tumours to allow less extensive surgery. While preoperative radiotherapy for the intact tumour is not standard practice at present, it is possible that this may have a role in the future (if validated in clinical trials) in association with neoadjuvant chemotherapy or hormonal treatment to shrink tumours and allow more patients to have breast conserving surgery rather than mastectomy.

While many solid tumours can be effectively treated with radiotherapy, some tumours are resistant to such therapy. Low oxygen levels (hypoxia) are an important contributing factor to radio resistance (Begg *et al.* 2011). However there are currently no clinically applicable tools to measure the dynamic spatial changes in tumour hypoxia. It is estimated that approximately 40% of breast cancers are hypoxic and the use of implanted biosensors to capture real time data on changes in the cancer tumour microenvironment could provide information on the tumour's resistance to radiotherapy. This is an important gap in knowledge and a research priority (Eccles *et al.* 2013). The tumour microenvironment is the cellular environment of the tumour, including surrounding blood vessels, immune cells and the extracellular matrix (ECM). In the metastatic process the primary tumour and its metastatic sites are of critical importance to the spread of the cancer (Joyce and Pollard, 2009). An embedded biosensor with the potential to produce data on the tumour micro-environment that are precise in both space and time, could be used to target X-ray dosage to hypoxic areas of the tumour, thereby maximising its effectiveness.

For regulatory purposes, a biosensor can be considered an active medical device when it is an instrument which, together with its software, can be used for diagnostic and therapeutic purposes, relying on a power source other than that generated by the body. The Active Implantable Medical Devices Directive (1993) AIMD 90/385/EEC as amended by Directive 2007/47/EC) defines an active medical implant as:

“...any active medical device which is intended to be totally or partially introduced, surgically or medically, in to the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure”.

Real time data on tumour chemistry and biology can be used to identify optimal scheduling of delivery of radiotherapy and chemotherapy, with major implications for cancer treatment services to accommodate this scheduling. Targeted radiotherapy can also help minimise the side-effects that some patients suffer, ranging from temporary ailments such as dry mouth or mouth ulcers (in the case of head and neck cancers) to pneumonitis and cardiac damage (in the case of breast cancer). By concentrating on killing cancer cells and minimising damage to normal tissue, targeted radiotherapy has the potential to minimise these side effects (Begg *et al.*, 2011) by avoiding unnecessary irradiation of normal tissues. For the type

of 'lab-on-a-chip' development that is the subject of this paper the ability to use wireless power and communications, as is the ambition for this device, has been demonstrated by Johannessen *et al.* (2004) and Smith *et al.* (2007).

There are two main potential applications of this biosensor (see Appendix 1):

1. Inserted prior to surgery to take real time measurements about the biology and chemistry of a patient's breast cancer and then subsequently removed during surgery along with the tumour.
2. If patients do not require surgery to treat their breast cancer, the biosensor could remain in the body during treatment as part of a personalised treatment regime, and thereafter any wires or ancillary devices would be removed, but not the devices themselves.

This qualitative study explored the views of breast cancer patients about implanted biosensors through a series of semi-structured interviews with 32 women who had successfully completed a course of anti-cancer treatment. There is a dearth of published literature on the views of cancer patients on the risks and benefits of tumour biosensors to personalise radiotherapy treatment.

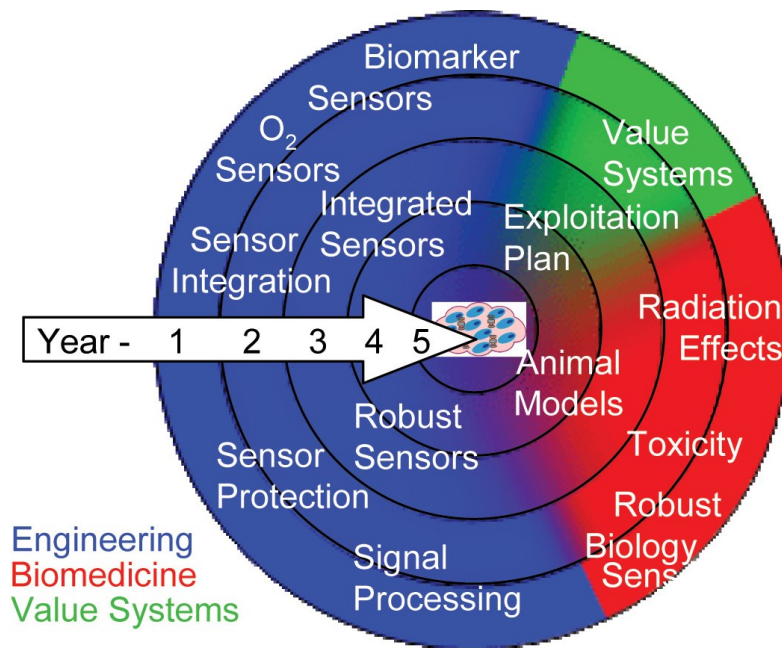
The research reported here was conducted as part of the University of Edinburgh IMPACT project (Implantable Microsystems for Personalised Anti-Cancer Therapy) (www.eng.ed.ac.uk/impact) funded by the Engineering and Physical Sciences Research Council (EPSRC), involving a project team consisting of engineers, chemists, veterinary clinicians, social scientists and human cancer specialists, led by Prof Alan Murray. Figure 1 summarises the components of the overall project and this report is part of the social science work package that is considering patient acceptability, changing regulation and possible barriers to commercialisation, and developing a strategy to implement uptake of the new technology if and when proof of concept can be demonstrated. The views of recovering cancer patients, as described here, will be used to inform future decisions on the design of the device.

2. Methods

2.1 Sampling:

The study adopted a purposive and convenience approach to sampling, recruiting on the basis of cancer type and outcome of cancer treatment (only breast cancer patients who attending a post radiotherapy review clinic were approached). Forty such patients were expected to be on follow-up in any one-month period and the study lasted 3 months, which would potentially offer a sample size of 120 patients. The target sample size of 30 was therefore feasible even if a low up-take rate of 25% occurred, and achievable within the time-frame of the study. During recruitment, the actual number of patients on follow-up who met inclusion criteria was lower than expected, which led to extension of the time-frame for data collection.

Figure 1. IMPACT Project



2.2 Recruitment

The recruitment rate was 73% and 32 women were recruited to the study. Involvement in the study was on an opt-in basis. Potential participants were identified and screened in the first instance against the eligibility criteria by four consultant clinical oncologists specialising in breast cancer at the post radiotherapy clinic at the Edinburgh Cancer Centre, Western General Hospital, Edinburgh.

Inclusion criteria

- Diagnosed with breast cancer – pre metastases stage
- Over 18 years of age
- Successfully completed anti-cancer treatment (i.e. those in post-treatment recovery)
- Ability to consent
- Ability to take part in an interview in English language

Exclusion criteria

- Vulnerable/ unsuitable patients (as screened by consultant/specialist nurse)
- Patients who are taking part in other studies at the time of recruitment
- Inability to consent
- Inability to take part in an interview

Dependent on the consultant’s judgement of the suitability of the patient they introduced the research to their patient during a scheduled appointment. If agreeable the patient was then introduced to the researcher, who explained the study and gave the patient the participant information leaflet and consent form (Appendix 2). The patient was asked to return home and consider the invitation. If patients were still interested after reading the participant information leaflet in their own time, they were asked to fill in the form and post it to the researcher at the University of Edinburgh (a prepaid envelope was enclosed in recruitment packs).

Once the researcher had received the consent form with the patient's details, she contacted the patient enquiring whether they were still interested in taking part in the study. The researcher answered any further questions and emphasised that participation is voluntary, and patients are under no obligation to participate. The researcher also explained that participants were free to withdraw from the study at any time, without giving any reason, and without their medical care or legal rights being affected. Following this, a suitable date and time for the interview was arranged. This study was conducted in accordance with ethical approval received through the NHS Lothian Research Ethics Committee (REC reference number 10/S1103/41).

2.3 Research questions

This study used qualitative semi-structured interviews to investigate patients' views of implanted biosensors, (Appendix 3). The semi-structured interview format allows for flexibility, while providing a general structure to ensure focus on the research questions (Flick, 2009). The following research questions included consideration of possible technological issues related to the development of the IMPACT device:

- Views (both positive and negative) regarding the use of implanted biosensors.
- The acceptability of different shapes, sizes and insertion techniques and the levels of discomfort they may cause.
- The length of time for which it is acceptable to retain the sensor (days, months, years).
- The risks attached to insertion and use of the biosensor.
- Views on the security of data transfer from the sensor to computers or databases, including storage, use, and access to data.

Considering the wider research environment on the use of implanted devices, converging technologies such as biosensors (Swierstra *et al.*, 2009) bring together biotechnology, nanotechnology and information technology, yet in doing so do they may diminish the cogency of the functions and/or bring additional risks. For example, as demonstrated here, where the sensor is able to transmit data about the tumour to a monitor outwith the body, there is a need for accuracy, reliability and integrity of measurement and also issues of data security and accuracy. Other challenges are related to the size of the sensors and how well information can be transmitted as the smaller the sensors the more difficult it is to transmit data from within bodily material and tissue. However, miniaturising the sensors allows them to be more easily injected into the body. Size also matters when it comes to the battery which requires to be large enough to power the sensor but at the same time small enough for insertion. Relatedly, protecting the sensor from the body's immune system and from bio-fouling may impede information collection and transmission. Hence there are tensions between what is clinically desirable, what is feasible in engineering terms and what is required in governance terms. Information was provided to patients (Appendices 2 and 3) to outline the key points of the study, its overall aim and highlight potential risks and benefits of the use of the proposed device. Complex issues related to the size and insertion of the device (Figure 2), power options (Figure 3) and data transmission options (Figure 4), and were presented using illustrations. At the time of biosensor development there were three possible options for powering the device and three for transmitting the data. Participants were shown these illustrations and asked about their preferences.

Figure 2. Size and insertion of the device.

Expected Size of the Sensor



Method of Insertion

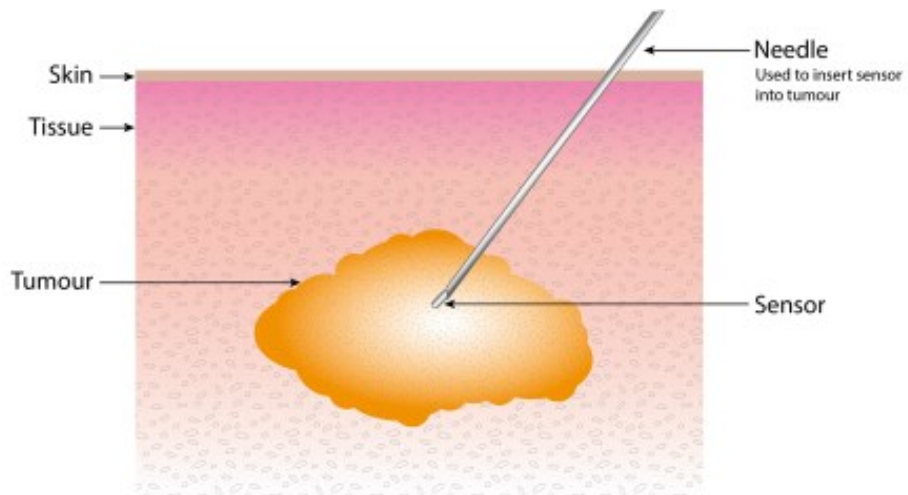
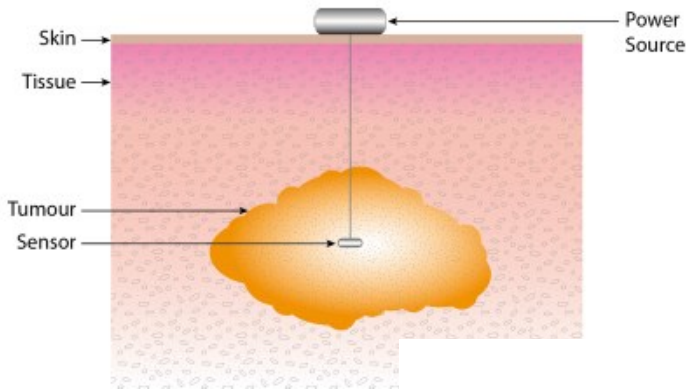


Figure 3. Power options.

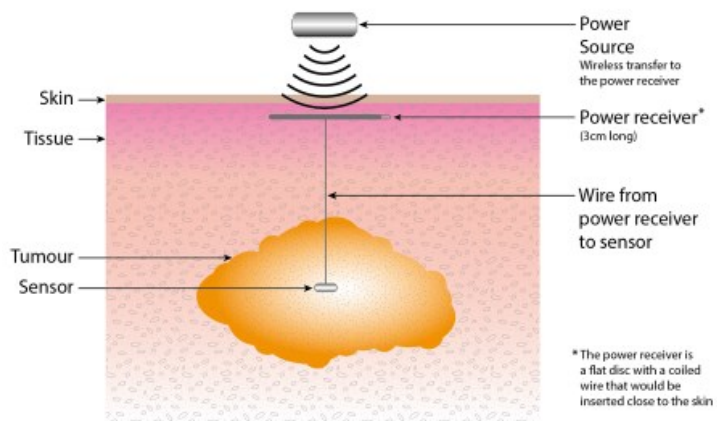
Power Option 1



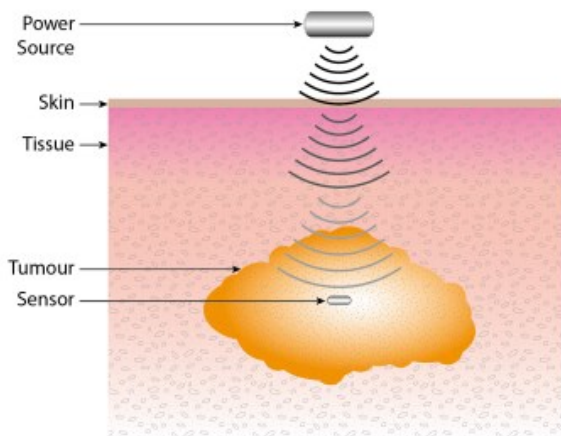
Power Option 1 would have a power source sitting on the skin, wired to the sensor.

Power Option 2

Power Option 2 would involve both a wireless and wired component. Power would be transmitted wirelessly to a receiver just below the skin. The receiver would then transfer the power along a wire to the sensor. The receiver may be approximately 3cm long.



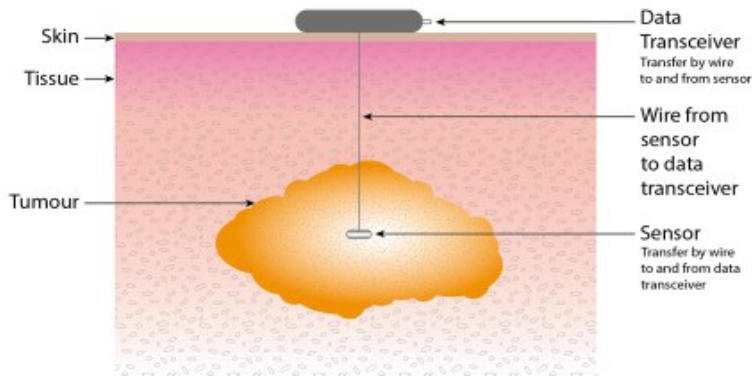
Power Option 3



Power Option 3 would be a completely wireless option.

Figure 4. Data transmission options

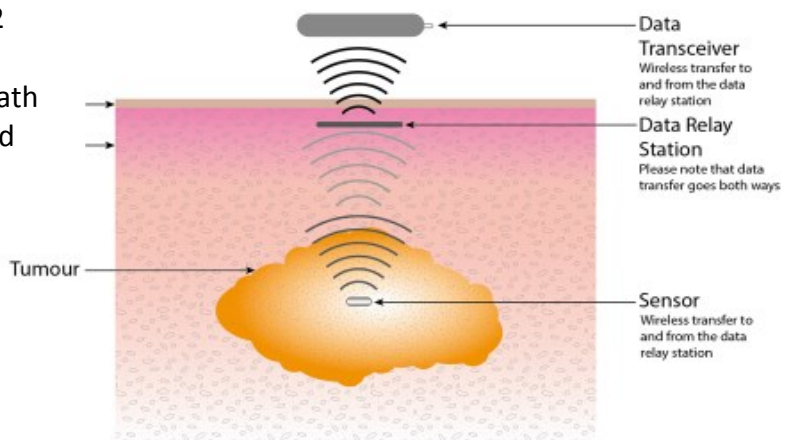
Data Transmission Option 1



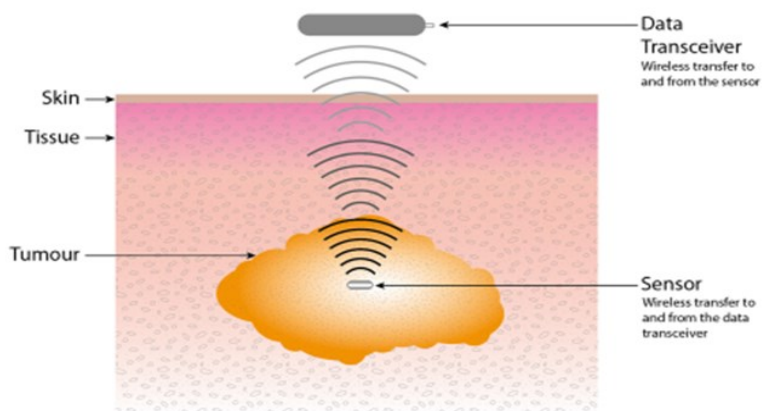
Data Transmission Option 1 would have a data transceiver sitting on the skin with a wire from the sensor relaying information back and forth.

Data Transmission Option 2

Data Transmission Option 2 would involve a data transceiver sitting underneath the skin relaying data to and from the sensor wirelessly.



Data Transmission Option 3



Data Transmission Option 3 would present a wireless option.

2.4 Interview process

Overall, 32 post-treatment breast cancer patients took part in an interview. Most interviews lasted approximately one hour. Before the interview, the researcher discussed the participant information leaflet and the consent form. Participants were informed how data would be used in a report and possible publications and permission to record the interview was sought. Before commencing the interview, each participant was given the opportunity to ask any questions and then asked whether they were happy to take part in the study and, if so, to sign two copies of the consent form (see Appendix 2), one copy of which they were given to keep.

The intention was to interview patients about their views of implantable biosensors in light of their experiences of breast cancer but we did not want them to relive previous circumstances in an experiential and unduly upsetting manner. The interviewer paid close attention to any signs of this or general fatigue during the session. If patients appeared to be fatigued, the interviewer offered them a break and checked whether they were happy to continue with the interview. None of the patients demonstrated any visible distress or tiredness during the interview or in the time after. In fact, many patients continued talking after the interview was completed and invited the researcher to stay. A summary of the research was offered to the participants.

2.5 Data management, analysis and feedback

Interviews were recorded with a digital recorder and uploaded to a secure folder on the university hard drive. They were then transcribed and anonymised. Transcripts were managed and analysed using the qualitative data analysis software package QSR Nvivo 10. Given the lack of previous research on patients' views about implanted biosensors, the analysis followed a grounded theory approach, using an inductive approach to data analysis, i.e. conclusions were directly driven by the data. Data analysis followed a constant comparative method and used an iterative pattern of data collection, reflection/ analysis, further data collection, further reflection and analysis, and finally synthesis (Glaser and Strauss, 1967; Boyatzis, 1998). Following each interview, recordings were listened to and transcripts read several times in order to become closely familiar with the data and to gain an overview of the range and diversity of data (Ritchie and Spencer, 1994). During this stage, a list of key ideas and emerging themes was developed (Ritchie *et al.*, 2003). Following this familiarisation stage, a thematic coding framework was constructed. This first-level thematic coding framework was discussed and further refined and developed by the research team. During this period, coding was conducted manually, as this is seen as sufficient to gain an overview of key themes (Arksey and Knight, 1999). Once the thematic coding framework had been identified, it was applied systematically to all data. At this stage, Nvivo 10 was used to facilitate coding, thematic development and data retrieval. Finally, themes were compared within and across cases, followed by a process of interpretation, categorisation and theorisation. Findings were grounded in the data and help to explain the range of post-treatment breast cancer patients' views about implanted biosensors.

3. Results

3.1 Patient demographics and breast cancer experience

Participants were aged between 39 and 87 years; mean age 62 years. Two thirds of participants were married or had a partner, and one third were either widowed or separated. The majority had children (and grandchildren). In terms of how the breast cancer was detected, there was an almost equal split between self-referral/ finding a lump and routine mammograms (Table 1). The majority of participants had been treated by surgery adjuvant radiotherapy and hormonal therapy after breast conserving surgery or mastectomy. Only a few had received chemotherapy.

Table 1. Demographic characteristics of the sample

Participants in sample (n=32)	Frequency	Percentage
Age		Range:
Mean	62 years	39-87 years (SD=11.6)
<50 years	3	9.4%
51-60 years	10	31.2%
61-70 years	10	31.2%
>60 years	9	28.2%
Gender		
Female	32	100%
Marital status		
Married/partner	22	68.8%
Widowed/ separated/ single	10	31.2%
Family status		
Children/grandchildren	24	75%
No children/ grandchildren	8	25%
How was breast cancer found		
Screening mammography	17	53.1%
Found lump/ self-referral	15	46.9%
Breast cancer treatment received		
Surgery & radiotherapy	25	78.1%
Chemotherapy, surgery & radiotherapy	6	18.7%
Chemotherapy & surgery only	1	3.2%
Total	32	100%

3.2 General views of biosensors

Of the 32 patients interviewed, almost all (n=30) were in favour of (hypothetically) allowing a biosensor to be used during treatment:

I suppose, we're talking about potentially saving your life. I don't see why anybody would not want to have whatever you need to have in order to get a result. So no, it wouldn't concern me at all. (Participant 9, 52 years old)

Most patients were extremely positive, especially if the biosensor technology was endorsed and recommended by their health care professional:

I'm not like you young ones, you have minds of your own, I just believe in doctors and let them do. (Participant 6, 64 years old)

Absolutely, 100 per cent. If they said, we'd like to put this in, we think it will do this to improve your treatment or make your treatment quicker or less painful or cheaper or whatever, as long as there's clearly a benefit between doing it and not doing it, I'd absolutely do it. (Participant 12, 53 years old)

Yes, if it was passed and it was recommended as a treatment I wouldn't object to it at all. I would go ahead with it. (Participant 15, 75 years old)

Yes, I would use it if my doctor suggested it. (Participant 23, 56 years old)

Perceived benefits went beyond the individual patient, and often included family members or the wider community of people who may use the technology in future:

Well, I've got two granddaughters, I've got a daughter and daughters-in-law and if it's going to help anybody in the future - I thought, anything that's going to help anybody else, really. (Participant 20, 67 years old)

I think if something's going to help and it's going to help others in the future, that's the main thing. (Participant 1, 72 years old)

As one participant emphasised: When people have a growth in their body they want rid of, they'd gladly do anything. I don't mean that but you know what I mean, people want to get better. That's their main concern. (Participant 2, 78 years old)

3.3 Risk, doubt and complications

Two patients were unsure whether they would accept use of a biosensor. This was not because of the risks but mainly because they were unconvinced with how it would fit within the timeline of their treatment/surgery:

See that's quite a hard one to answer in my particular case, because from diagnosis to surgery was only two and a half weeks, so, you know, would there even have been time to do anything in my case, I don't know? (Participant 11, 43 years old)

Patients acknowledged the discomfort associated with inserting the biosensors and the potential for complications, such as an infection, allergic reaction or in extreme cases an embolism. Approximately half of patients (N=18) stated that they would want to know more about the likelihood of a complication or risk occurring. If the potential for complications was low (as evidenced by thorough testing of the biosensors), patients would be willing to have biosensors implanted as part of their cancer treatment:

I think if you were able to give sort of some statistics around that, but then again, until you start using this you can't give...like if I was the first person you were going to use it on, then I would just have to take the risk, I guess. It depends on where you are, if it was five years down the line, then you'd have plenty...well only one out of five million people, you'd be like, okay I'll take that risk. But I think it depends on what the risk is and how to quantify that, I guess. (Participant 18, 39 years old)

I would want to know what the percentages were, so that you know what you're playing with. And I'd want to know what the signs were for early detection of an embolism. And I think as long as you're aware of all of those things, you can make an informed decision. But, I mean, there were a lot of risks associated with all the other

treatments as well, including embolism actually, that you have to just outweigh the benefits. (Participant 21, 40 years old)

3.4 Size and shape

When discussing the potential size of biosensors, patients tended to accept any size. Their focus was on 'whatever helps to get better' reiterating the current theme of recovery from cancer:

Interviewer: If you look at the different shapes, you know, which one would you choose?

I wouldn't choose, I would leave it up to trust the doctors to know what they're doing. I'm not knowledgeable enough to comment on that. (Participant 15, 75 years old)

Some did express a preference for a smaller size however.

The smaller the better. (Participant 7, 51 years old).

Certainly some were keen on the idea of making the biosensors as small as possible, because it was perceived as less painful especially during insertion.

In terms of shape of biosensors, there was a 'once it is in what difference does the shape make?' philosophy expressed. As one participant put it,

Once it's in the body, you wouldn't really know it. (Participant 17, 65 years old).

When preferences were expressed the emphasis was on a smooth surface with a long shape and rounded edges,

Instinctively when it's got a curved end you think it'll be less sore going in. (Participant 7, 51 years old).

I guess the size and the shape would only matter in terms of the size and shape of the tumour ...Only if it was gonna make the insertion more difficult or more straightforward. (Participant 16, 64 years old).

Although pain on insertion seemed to affect views, again, emphasis was placed on the benefits of using biosensors and recovery:

I suppose when you actually think about the process you've already gone through, and you had the needles with the biopsies and everything else, in my mind, if it's going to cure me or help me get rid of cancer. It may not cure you in the long run. I don't know. But then, to my mind, you just get on with it, and it might not be pleasant, so if that was the best treatment for me I would say yes, go for it. I might not like the needles but...I didn't like the chemotherapy either, but you just do it don't you? (Participant 5, 57 years old, emphasis added)

Interviewer: How would you feel about having something like this inserted with a needle?

*Nervous, I'd be nervous, but it would just be **one more thing that you had to deal with. You would just deal with it, I can assure you.** (Participant 18, 39 years old emphasis added)*

In these two quotes there is an indication of the stoicism required when undergoing treatment. These women 'deal with it' and 'get on with it'. Willingness to have the biosensor is positive and based in trust in medical systems but is tempered almost with a degree of resignation and ambivalence.

3.5 Number of biosensors

A small number of patients expressed concerns about having more than one biosensor inserted:

I think I'd draw the line at probably three, I would think. But again, it would depend on the tumour and everything like that, I suppose. Because you can only talk from personal experience. I don't...in a way, I'm just thinking of myself, but...yeah, maybe three, yeah. (Participant 27, 62 years old)

However, most patients would agree to have more than one biosensor inserted if this was necessary for their treatment and recommended by their health care professional.

Interviewer: If they were put in by needle, would it bother you having just the one put in or having up to six or seven?

No, you've got to go with the flow. Put a face on, as Mother would say, but tremble inside. No, it wouldn't. It's all for a good cause. That's what it's all about. (Participant 6, 64 years old)

The following participant associated having more biosensors implanted with being more closely monitored.

Again, to me it would give me peace of mind to know it was being monitored regularly. (Participant 17, 65 years old)

3.6 Duration of biosensors in the body?

The women in this study tended to be pragmatic about the length of time the device was left in the body. If it was small enough, and 'it was doing its job' (Participant 7) and the biosensor could not be felt, then most were unconcerned about leaving the biosensor in:

As long as they're not doing any more damage, then, yeah, you're not going to know they're there or you will know they're there, but you wouldn't feel them or anything so, yeah, I would say if it's going to make your treatment better then, yeah, I'd be happy for them to be there (Participant 11).

I don't think it would matter. I don't think it would matter if it was in forever. I mean, you have implants put in, don't you. I didn't, they used the fat, but people do have implants put in. People have heart, cardiac things put in, don't they, and tubes to replace things that aren't working. As long as your body is not rejecting them and it's not causing any problem, you're just not going to know it's there. People have, as we've talked about, contraceptive implants in their arm, don't they, for years (Participant 21, 40 years old).

Trust in health care professionals could sometimes override patients' individual opinion and preference, as illustrated in the following quote:

I would just go on whatever the doctors recommended. That's not my area of expertise so if they said you need to keep it in for 3 months or six months or six years or like with

the Tamoxifen, for example, I'm not happy to take that for ten years, but that's what I'm told to do, so that's what I'm going to do. I would just be guided by whatever the medical profession felt was necessary.

Interviewer: What if you had any side effects, like say the tablet you are asked to take for ten years?

I do have side effects. I don't like them, but what can you do? It's potentially saving my life, so you just have to adapt (Participant 9, 52 years old).

Again, patients had to be stoical and 'have to adapt'. But again, a minority were wary with having something 'foreign' inside them:

Interviewer: I mean, would you worry about having them in if they did stay in for longer, what would you not like about it? If you couldn't see them or anything...

It's just a foreign body.

Interviewer:...and if you couldn't see them, if you couldn't feel them, you know. I'm just wondering what are the...

Just because it's a foreign body, and it's not really meant to be there. And if it's there, it's only, in my opinion, if it's there it's there for a reason, and if that reason is now redundant then there would be no need for them. If it came to the bit where they say, you know, they have to remain in, then I would just accept that that was the case.

But if it was the option to remove them, then I would probably want it removed (Participant 31, 53 years old).

3.7 Power and data transmission options

If a preference was expressed on the power and data transmission questions, then the majority of patients (N=28) favoured a wireless option when it came to both the data transmission and power options (see Illustrations 1 – 3, above). Wireless was perceived to be more convenient, advanced and less visible on the surface of the skin. Patients also considered the practical implications of having visible wires on the surface of the skin. The wired option was perceived as more obtrusive, especially when getting dressed. It seemed important not to have anything visible on the surface of the skin as this was seen as a way to facilitate coping with cancer treatment.

Option three certainly seems to be the best one, because then you can always forget it's there, you see. And for me personally, for survival, I think it's good to try and almost forget something that you have it, that you don't dwell on it, dwell too much on it when you have cancer. (Participant 27, 62 years old)

Because it's got that and nothing else. And if that was, for some reason, not technically possible in all cases, then that [option 2] would be better than this one [option 1]. Because it would be...you wouldn't necessarily be conscious of it, you know, it wouldn't be something you could see, you could kind of forget about it. (Participant 16, 64 years old)

[Option 3] It's less obtrusive. [...] Simply because there's less erm stuff, less bits inside you. (Participant 31, 53 years old)

Option one you might see it. Option two it's going to be trickier, the insertion process. The wireless sounds good to me. (Participant 23, 56 years old)

Three patients preferred option 2. No one favoured option 1.

3.8 Data security

In general, patients did not express concern around data security. This was either because patients assumed that data security was being taken care of by the National Health Service and the medical professionals in charge of the biosensors, or they did not think that the data could be of interest and use to anyone. Some patients compared the data to the confidentiality of their personal financial information and bank details concluding that readings from the biosensors would be a lot less valuable and interesting to other people:

I use a bit of data security when I'm talking about my bank, but when I'm talking about the status of my tumour, I don't care who knows. Anybody...if I'm transmitting it to the world, I don't care. (Participant 12, 53 years old)

One patient suggested that the data may be of interest to insurance companies however:

It is a concern, but really, I don't see what other people could do with it apart from the insurance companies or something. Learning about your medical stuff, that would be one of the concerns, I suppose. (Participant 3, 57 years old)

In most cases, patients were also looking at the 'bigger picture' and their main concern was on getting the best treatment available and being able to recover:

I wouldn't worry about it. No. I'm sure a lot of people wouldn't worry about that either, it could be the least on their minds to worry about that. When you're going through cancer itself, just the diagnosis itself, you wouldn't be thinking about that; you'd just be thinking on how good this sensor and technology is that it can actually give a reading; and it's for your benefit. (Participant 25, 56 years old)

4. Discussion and conclusion

To our knowledge this is the first report in the literature describing the views of patients treated for breast cancer on the potential benefits and risks of implanted tumour biosensors to individualise radiotherapy treatment. The development of any technology should ideally be based on social, group and individual acceptance of it.

There are also few previous studies on patient or public acceptability of implantable biosensors although there is some research about views of various medical devices implanted irreversibly into body tissues that could offer a precedent to inform how patients or publics might react to such biosensors. Cochlear implants, for example, are implantable electronic devices that are used in patients unsuitable for hearing aids. Lack of prior consultation meant that development of this technology in the eighties met with, and continues to meet with, varying degrees of resistance and rejection by some members of the deaf community (Blume, 1999). Studies of implantable cardiac defibrillators (ICD) report that insofar as the patient has a foreign object inserted into the heart (Duru *et al.*, 2001) living with an ICD can cause significant psychological distress with anxiety being both a prerequisite to and consequence of 'device shock' (Asad *et al.*, 2014; Birnie *et al.*, 2007; Bunch *et al.*, 2004; Bunch *et al.*, 2008; Duru *et al.*, 2001; Green & Moss, 1969; Sakensa, 1994; Tchou *et al.*, 1989; Vriesendorp *et al.*, 2013; Yuhua *et al.*, 2012).

An examination of existing literature on user acceptance (Wilkowska *et al*, 2010; Scheermesser and Rashid, 2008) and the empirical data generated, Schaar and Ziefle (2011a, p514) suggests that acceptance of medical technology is "... complex and strongly affected by health status, age, gender roles, culture, personal living conditions or care situation".

Two important contextual factors in this research influenced the positive views expressed about the hypothetical insertion of biosensors: 1) the experience of being in recovery from breast cancer; and 2) trust in the health professionals involved in the successful recovery. The consensus was that most informants would welcome implantable biosensors as part of future cancer treatment. Participants saw clear benefits of improved treatment and potentially reduced side effects when using biosensors to personalise and tailor cancer treatment.

On the one hand, due to their cancer experience and their contact with the medical profession, there was overall willingness in this sample to have a biosensor inserted. The cancer experience was a reason for recruitment to this social science study and we expected views of biosensors to be positive because of this. There may have been an unexpected influence on patients' views arising from treatment options, depending on whether the women had had surgery during their breast cancer treatment. Future use of biosensors could contribute to more breast conservative treatment options. If a patient had had surgery to remove their breast cancer, by the time of interview this could influence their views of having a biosensor implanted, particularly if the biosensor could increase the efficacy of radiotherapy to the extent that future patients would not require surgery. There was no evidence of this effect from this study, but this may be something to consider in any future, larger scale projects.

Some studies have shown that women are likely to report higher levels of body image concerns than men in ICD studies (Starrenburg *et al.*, 2014). Although the ICD is implanted above the breast it leaves an imprint on the skin where the device can be felt when pressed. Patients discuss how, regardless of gender, the imprint of the device on the skin served as a reminder (Pollock, 2011 p100):

"Every time I look in the mirror I think, oh, you've got an ICD in your chest. There's a physical manifestation of what happened to me. It's something that happened inside my body, but I can see it every day when I take a shower. I look in the mirror and I see a little lump. Yeah, I think about what happened to me every day."

Biosensors will not be felt nor will the patient be aware of them unless there is a wired connection through the skin or an imprint where the transmitter will sit under the skin as with an Implantable Cardiac Defibrillator or pacemaker. Implanting devices into areas of the body sensitive to ideas of femininity, e.g. breast, does raise questions about the impact on body image. Positive willingness to have a biosensor did not appear related to concerns about inserting technology into the breast – an area associated with female sexuality and femininity.

The majority in this sample were not under forty years old and there was some indication that with increasing age there is more likely to be: 1) increasing trust in the medical profession; and 2) less concern about the aesthetic and cosmetic effects of implantation. No one preferred the wired option regarding power or data transmission and the vast majority preferred the wireless option. This dislike has also been found in other research relating to

implantable cardiac devices (Pollock 2011). It seems that, if implantable medical technologies are not fully implantable, the skin disruption serves as a reminder of the disease. It would be worthwhile to investigate further this dislike of technology that breaks the skin, or at least imprints on it.

If a biosensor enhances treatment then the willingness to have one is 'rational' - who would not want to recover from cancer? But the experience of benefiting from it adds to the list of treatments that have to be undertaken and adapted to. Despite the overall enthusiasm for the sensor there were also some indications of doubt and reticence. Some women in this sample were reticent about being the first to clinically trial the technology as well as expressing concern about the pain that might accompany the insertion of the biosensors. There was also mention in a few of the accounts that patients had to 'put a face on it' and 'you just deal with it'. Ambivalence is therefore an under-current in some accounts that indicates that for this sub-group of the population, treatment and interventions are events that have to be borne. Trust in the medical profession appeared as a 'blind faith' in the decisions that were being made on their behalf – as a patient 'you have to follow advice' and 'go on whatever the doctors recommended'. However, this did not eradicate the ambivalence implicit in some of the accounts regarding using the technology. Interestingly, women who expressed concerns about the risks involved tended to be a younger cohort. They did not articulate concerns about aesthetics but appeared to be more risk aware (or averse). This is not to suggest that all young women recovering from breast cancer will be more risk aware about implantable technology but may suggest that those who are more risk aware may tend to be younger. This cannot be established from this study.

Results from an exploratory interview study about biosensors with 12 men in remission from prostate cancer, (Haddow *et al.* 2015 (in press)) indicated unanimous agreement to the scenario of having a biosensor inserted. Trust in the medical professionals as well as the experience of having had cancer were important factors in the expression of positive views. Some informants expressed a preference for the mechanics of the device (smaller size, number and no obvious visibility). Despite mention of willingness to have a biosensor there was also ambivalence expressed in that the men felt this was something they would 'have to get used to', as with the patients in the survey reported here.

Little concern was expressed about data transfer from the device. However, these results should be interpreted with caution. It is unknown whether the results from this previous study were unique to male participants concerned about an organ, the prostate, found only in men. In addition the sample size of this pilot was small and may not have reflected the broader population of men treated with radiotherapy with curative intent for prostate cancer.

In the research reported here, interviews with breast cancer patients in recovery highlight both an alternative view point to prostate cancer patients as well as exploring reactions to inserting implantable medical devices into areas of the body that have particular significance for feminine identity. Further there are key differences related to the practicalities of using the biosensor between prostate and breast cancer patients. With breast cancer the biosensor may be removable, and inserted for various lengths of time, e.g. during radiotherapy treatment. This is not the case with prostate cancer where the biosensor would have to remain in the body due to the inaccessibility of the organ – i.e. men in the prostate study had experience of living with fiducial markers in their body.

The implications of this study of breast cancer patients for the IMPACT project appear clear.

- Patients who have recovered from cancer are willing to have a biosensor(s) implanted as a way in which their treatment can be improved.
- Clear preferences are articulated regarding the avoidance of pain on insertion as well as full implantation without any wires protruding from the skin.
- There was no clear preference related to the number of sensors.
- Technological challenges relating to removal of the sensors do not appear important and neither does security of the data.
- The preferences for wireless, small size and smooth shape might prove the most challenging for development of the technology, but for patients these may be strategies to lessen the physical and psychological pain that accompanies treatment that has to be undergone when living with cancer.

These social science data have been generated from a sizeable cohort of participants, and the emergent themes compare favourably with data from research with prostate cancer patients (Haddow *et al.* 2015 (in press)). Missing from these breast cancer accounts are the views of those who: 1) are from a much younger cohort; and 2) have metastatic breast cancer. Younger members of the public are part of a generation termed 'digital citizens' who may have different views regarding the security and use of data from participants in this research. It is envisaged that further research with additional groups of patients may offer additional insights, if required, into the IMPACT project.

It should also be borne in mind that patients may have had difficulty in conceptualising how exactly biosensors might affect them since these devices are still at a very early stage of design. However the illustrations presented to patients of the possible alternative designs and sizes of the possible prototype biosensors appear to have been helpful in grasping the principles of biosensor design, implantation and function.

The views of cancer patients who have successfully completed their anticancer treatment are important as they may provide a guide to the acceptability of implantable diagnostic devices when used in groups of cancer patients in the future. The point of patient engagement, as in this project, is not to 'drive' the design process per se but to sensitise the designers to the preferences of the users. The results also demonstrate, to some extent, a prioritisation of the technological challenges as socially understood. This then is not only about patient willingness to benefit from a possible technological enhancement of treatment – to which the answer will only ever be positive – but to understand the challenges of living with what that treatment might mean.

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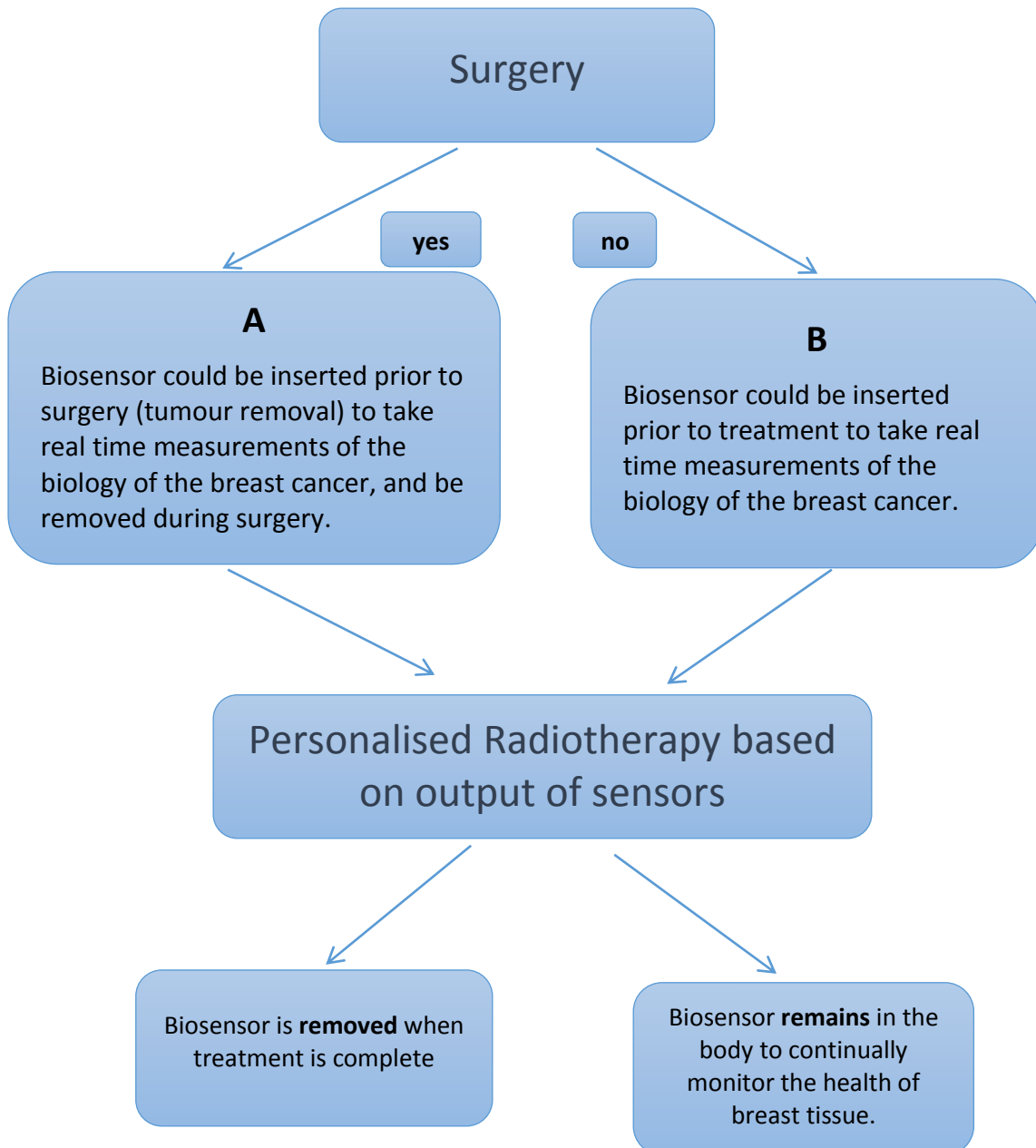
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Appendix 1: Potential uses of the biosensor in breast cancer treatment

Treatment can consist of one or a combination of treatments depending on individual circumstances (i.e. size, stage and grade of the cancer)



Appendix 2: Participant information sheet and consent form



31st March 2014

PARTICIPANT INFORMATION SHEET (PIS) BIOS V.4

INNOGEN CENTRE

Science, Technology and Innovation Studies

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Seeking your views about future monitoring and personalizing of cancer treatment

We are inviting you to take part in a research project about your views on future ways of monitoring and improving cancer treatment. These monitors (called biosensors) are tiny devices that are at a very early stage of development in research. However, if once developed, they were found to be safe and effective, one or more might be inserted into a patient's cancer at some time in the future. They will be designed to measure the cancer's biological activity in real time. This information has the potential to individualise radiotherapy treatment and improve cure rates. **WE ARE NOT ASKING YOU TO TEST ONE OF THESE MONITORS (biosensors),** and we are very grateful for your thoughts.

My name is Theresa Ikegwonu and along with my colleague Gill Haddow, we are social science researchers working at The University of Edinburgh. We have talked about this technology with men who are in recovery from treatment of prostate cancer and we now would like to talk with 30 other individuals like yourself who have had their cancer removed and undergone radiotherapy treatment for breast cancer.

Before you decide whether or not to take part, it is important for you to understand why we are doing this research and what it will involve. Please read this leaflet carefully and, if you want, discuss it with others. This leaflet tells you the purpose of the project and what will happen if you decide to take part, and gives you more detailed information about the running of the project. Please ask us if there is anything that is not clear or if you would like more information – our details are at the top. Finally, thank you for considering our invitation.

WHY IS THIS STUDY BEING DONE and WHY ME?

Biosensors are tiny devices currently being developed in order to assess, in real time, the cancer environment. Such cancers can be effectively treated with radiotherapy. However, there are variations in response to treatment. It is hoped that these biosensors will be able to monitor the cancer and use this information to individualise radiotherapy treatment and to maximise the killing of cancer cells.

So this study is being done to explore the views of a variety of patients with early breast cancer who have received radiotherapy. This is why we have approached you. We are working with cancer specialists at the Western General Hospital, Edinburgh who are especially interested in what you think about 'biosensors'. Although we are working in partnership with your consultant, we will be independent of them and they will not know whether or not you were interviewed.

WHAT WOULD PARTICIPATION INVOLVE?

Biosensors are currently being developed by scientists and medical professionals. WE ARE NOT ASKING YOU TO TEST ONE. What we want to do now is to interview you for approximately one hour seeking your views about this future technology. We will arrange this interview at a time and at a place that suits you best. This might be in the comfort of your own home or if more convenient, we can arrange to meet at the hospital. We know that you will not have thought about biosensors before and may not have even heard the word 'biosensor', but we will be able to explain what they are, what they might do and show you pictures of what they might look like and what size they might be.

DO YOU HAVE TO TAKE PART?

No - it is entirely voluntary. It is up to you to decide whether or not to take part. If you decide not to take part, you do not have to tell us why. You can make this decision at any point. If you choose not to participate, your medical care will not be affected in any way.

WHAT ABOUT TRAVEL EXPENSES?

It should not cost you anything to take part in this research, but if it does we will reimburse for reasonable local travel expenses by taxi or public transport.

CAN YOU WITHDRAW FROM THE STUDY?

Yes. You can withdraw from the study at any time without giving a reason.

WHAT ABOUT CONFIDENTIALITY?

The researchers do not have access to any information about you other than that you have provided to us. You will be asked for your written permission to pass your contact details on to us. This does not mean that you have to take part. One of the researchers will contact you to explain a bit more about the study and the interview. If you are still interested we will set

up a time, date and place where we can conduct the interview. With your permission, a recording of the interview will be taken because we need an accurate record of what we discuss. Once we have analysed the recording we will destroy it. We will make sure that you will not be identified. Anything you tell us will be treated confidentially. We can assure you that any reports or publications will not contain information from which you can be identified. We will be delighted to send you a short summary of the results from the study if you so wished.

WHAT HAPPENS NEXT?

A member of your oncology medical staff should have already approached you to make sure that you are willing for me to contact you about this study. If after reading this information sheet you would like to take part, we would like you to contact us. Please contact the researcher whose details are listed below and we will arrange a time and place that suits you best. Let us know if you require further information. Please read the 'Consent Form' carefully and you can bring it with you to the interview.

<p style="text-align: center;">Dr Theresa Ikegwuonu Innogen Institute Science, Technology and Innovation Studies The University of Edinburgh Old Surgeon's Hall, High School Yards Edinburgh, EH 1 1LZ Telephone (0131) 650 6389 or e-mail: theresa.ikegwuonu@ed.ac.uk or by post at above address.</p>

If you would like to speak to someone who is independent of the study, please contact Dr Steve Sturdy by phone (0131) 651 4741 or e-mail: s.sturdy@ed.ac.uk

If you would like to make a complaint about this study, please contact NHS Lothian:

NHS Lothian Complaints Team
2nd Floor, Waverley Gate
2-4 Waterloo Place
Edinburgh, EH1 3EG
Tel: 0131 465 5708.

Finally, thank you for your interest and for taking the time to consider this invitation.



Participant’s Consent for Interview (BIOS,V.4) –
(1 copy for the researcher, 1 copy for the participant)

“Talking about ‘implanted biosensors’ – what do you think?”

IF YOU AGREE WITH EACH STATEMENT, PLEASE WRITE YOUR INITIALS IN THE BOX:

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights or medical care being affected.

I have read and understood the Participant Information Sheet (PIS BIOS, V.4, dated 31st March 2014) and have been given the opportunity to ask questions.

I am not being rewarded financially or otherwise for my participation.

I agree that an audio record of my participation can be made.

I understand that direct quotes might be used from our conversations in reports or publications but my name will not be used in these.

I have had the opportunity to discuss this study and to ask questions.

I consent to be interviewed (PLEASE INITIAL BOX)

Please print your name in BLOCK LETTERS:

I _____ agree to take part in the above study.

Participant Signature _____ Date _____

Researcher Name _____

Researcher Signature _____ Date _____

Appendix 3: Interview schedule

Interview No: Interview ID: BIOS_BC_
Date of Interview: Interviewer:
Pseudonym used:

Pre- interview/ Introduction:

My name is (Haddow/Ikegwuonu) and along with my colleague (Haddow/Ikegwuonu), we are social science researchers working at the University of Edinburgh. We are working with cancer specialists at the Western General Hospital, Edinburgh who are especially interested in what you think about ‘implanted biosensors’. We know that you will not have thought about this before or maybe not even have heard the word ‘biosensor’ before, but we will be able to talk you through what they are and show you what they may look like. We will be talking with thirty other individuals like yourself who may have undergone treatment for cancer in the past about their views on this future technology.

So I am hoping we can chat for about 45 minutes to 1 hour (check if ok timewise). I do need to record our conversation but this is purely for accuracy of recall. I will download the audio recording which will be anonymised to protect your identity, before sending it to a trusted Innogen administrator who will transcribe it. The recording will be stored and treated confidentially in accordance with the Data Protection Act.

We really need to get your views on the development of this technology – both positive and negative (there are no right or wrong answers). What we need to know is what you think; your honest answers. We also appreciate that you may find it difficult to think about a device whose shape and size has not been finalised.

Would you like us to send you a short report about what we find? Is there anything you want to ask before we begin?

What made you want to take part in this research project?

SECTION A: Information about Interviewee:

Can I ask WHEN you were born?

Can I ask you where you were born?

Are you married?

Do you have any children?

Do you or have you worked?

Have you any formal qualifications (PROBE: biology, science, etc.)

Are you involved in any particular religion?

Do you happen to watch or read any science fiction?

Donate blood (if not why not)?

Willing organ donor?

How are you with needles generally?

SECTION B: ICE-BREAKERS:

Can we talk a little bit about your cancer treatment? Could you tell me about what treatment you received?

(If radiotherapy treatment received) Tell me about your radiotherapy treatment?

More specific questions about radiotherapy sessions (when started; how long; etc.)

Descriptions of radiotherapy treatment?

General views on (radiotherapy) treatment (time, comfort, side effects/ impact on everyday life)

If you had breast conserving surgery, did you have any metal markers inserted at the time of surgery?

Did you have (or are you going to have) any reconstructive surgery?

What type/stage of breast cancer did you have?

When did you complete your treatment?

Any other family members who had cancer?

SECTION C: INTRODUCTION TO BIOSENSORS:

Now I'd like to talk to you about the development of biosensors.

Have you heard the term biosensor before? (if yes, where and when?)

INFORMATION B:

Biosensors are tiny devices that can be inserted into a person's cancer tumour. They can monitor the cancer's biology and take real-time measurements (e.g. level of oxygenation, temperature, pH level). Oxygenation is the process by which concentrations of oxygen increase within a tissue. This information can then be used to individualise radiotherapy treatment.

Biosensors that can be used routinely do not yet exist. **We are not asking you to test one.** They are currently being developed by cancer specialists and engineers in Edinburgh. One or more would be inserted by a cancer specialist into the cancer. It is hoped that biological information (e.g. levels of oxygenation in the cancer) captured by the biosensors will be able to tell clinicians (i) which regions of a cancer need extra doses of radiation to eradicate cancer cells (ii) when may be the best time to treat the tumour. The main aim would be to maximise the effectiveness of radiotherapy against cancer cells. It might also identify patients unlikely to benefit from radiotherapy.

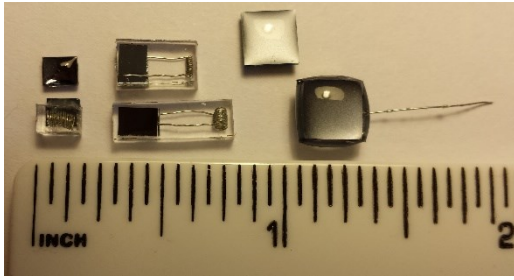
EXAMPLE: A biosensor that can monitor blood sugar levels in people with diabetes.

Is that clear to you – or do you want me to go over that again? Tell me, what immediately springs to your mind when thinking about this technology then?

Show physical models here (two smaller ones only). These are some examples to give you an idea of what the biosensor may look like.

As I explained before, the biosensor is still being developed and a process of miniaturisation will take place. The target is to make it the size of a grain of rice (show example of grains of rice).

Do you have any thoughts about the biosensor itself – about the way it looks for example? Do you think the size is acceptable?



PICTURE 1: Different shapes and sizes

What about shape of the biosensor, do you have any preferences?

Q. In future, there may be **more than one biosensor** (perhaps 6-8) implanted in order to gain more representative measurements in different regions of a cancer. Can you say what you might have a preference for (one or more sensors)? Is there any particular reason for this?

Q. Let's talk a bit about **method of insertion**. The biosensor(s) will be inserted by a needle. How would you feel about this?

Tolerances of Control

What would be the most acceptable and least acceptable from the following situations (MAKE SURE TO READ THESE OUT FOR TRANSCRIBER!):

INFORMATION C:

- The biosensor to be powered on by medical professionals and who can also switch it off.
- The biosensor to control itself and to be able to switch itself on and off in response to changes in the body.

At present our research team think the biosensor would be stationary embedded within the cancer tumour. It could be inserted before surgery (if you require surgery) and removed when surgery is carried out. How would you feel about having a biosensor implanted in such a way?

If you don't require surgery, it might remain in the body permanently. How would you feel about this?

Use medical illustrations to show different power options here

In relation to **powering the biosensor**, there are two options: it could either be powered remotely via wireless power transfer or using wires. If the biosensor had to have wires coming out of it in order to supply power, would that change how you felt about the sensor? Do you have any preference in terms of how the device is powered (select from medical illustrations- power options)? Why? Would you prefer the device to have wires/no wires coming out of it? Would it make a difference if the wires were hidden under the surface of the skin or were visible on the surface of the skin?

Q. **Duration** of biosensor in the body. How long would be an acceptable time to have the biosensor inside your body? (Prompt 24-48 hours, 1 week, 1 month, 1 year or indefinitely)

Use medical illustrations to show data transmission options here

Data transmission

There are a couple of options how data could be transmitted from the sensor to the data transceiver. Data transmission could either be through a wire or wirelessly (similar to power options). Which option do you prefer (select from medical illustrations- data transmission options), and why?

Q. Thinking about the transmission of information - What would be preferable – for the sensor to be able to transmit data:

1. for a short space of time and over a short distance only (in the clinic?) to a receiver that captures the data
2. To be able to transmit to the cancer centre from home (one off)?
3. To be able to transmit data to the cancer centre from home on a regular basis?

Probe: What are your views on **data security**? Any concerns? (during transmission and how it is stored)

If participant chooses different options in power and data transmission, check why (show them different cards with medical illustrations).

Q. There is a slim chance that the sensor could **do damage to the body**. It is an extra invasive procedure and there is always the risk of infection or an allergic reaction. Is that a risk you would take?

Q. **Thinking about the risks** again – there is an even smaller chance that the sensor could cause an ‘embolism’ that is, it could block an artery or travel to the lung causing a blockage, potentially leading to a person’s death. While the risks of a serious complication may be very small, is that a risk you would be willing to take?

Future Uses (Drug Delivery)

Q. It is possible that in the future, that the same biosensors could also be used to deliver drugs. Tiny wells in the device could hold small quantities of anti-cancer drugs. These could then be released directly into the tumour. Such smart devices might reduce the side effects of anti-cancer drugs (chemotherapy). This extends the medical value of biosensors. How do you feel about this? What are your views on this?

GOVERNANCE

If it was up to you, who do they think should develop and control the biosensors? (i.e. University researchers, private companies, NHS)

- Who do you think should ‘own’ the biosensor? Does it ‘belong’ to you? Is it part of you? (PROBE; before implantation, when it’s working inside the body? When it is no longer working/following completion of treatment? PROBE reasons for answer).

Development of the biosensor will be in compliance with regulatory guidelines: The biosensor is going to be regulated to make sure it is safe, it will be thoroughly tested and undergoing clinical trials.

- How important do you think it is for this technology to be developed? Should we be trying to speed up the process (as long as it is safe)?

COMPARING BIOSENSORS WITH OTHER MEDICAL INTERVENTIONS:

Just before we finish I want to ask you if you can think of any technology that exists at the moment that would be similar to the biosensor technology? Reasons why?

(Prompt: a thermometer, an X-ray, taking a pill, having a blood transfusion or an organ transplant, a pacemaker, hip joint replacement, artificial hand or leg, breast implant, contact lenses, hearing aid)

To finish: BENEFITS and RISKS:

- Overall, how likely are you to allow a biosensor such as this to be implanted?
- Is there anything that would put you off (try and get them to rank their concerns if they have any ...Patients are likely to be extremely supportive of medical progress).

Anything that we have missed?

Is there anything else you would like to say?

Any other comments or questions?