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The ethics of informed consent in novel treatment including a gender perspective

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[1] **R** = Report, **DEM** = Demonstrator, prototype, **DEC** = Websites, press & media actions, videos, **OTHER** = Software, technical diagram, etc

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Table of contents

1. Executive summary

Aims and scope: Informed consent (IC) is a highly regulated process through which a person voluntarily agrees to participate in research, after being informed of everything she or he needs to know. The current IC process has been shaped by international and national guidelines, developed over the last 70 years to ensure that clinical research upholds strict ethical and legal standards. Such extensive guidelines have however led to the introduction of long, complicated documents that are heavily reliant on technical and legal language. Not only does this approach discourage some participants from taking part, even those that do consent are often left with a limited understanding of the trial.

The main aim of this study was to examine the views and opinions of European patient groups on IC for clinical vaccine trials with a particular focus on the themes of comprehension, assent, patient expectation and gender. Patient groups have a unique insight into the perspectives and concerns of the patients they represent, and such views must be considered if we are to provide a comprehensive, multi-state holder perspective on the issues surrounding IC for clinical vaccine trials.

Methodology: Fifteen European patient groups were invited to attend a one-day workshop in central London, and nine accepted the invitation. Attendees represented eight patient groups, from five European countries. All were active organisations that directly represent patients, had a focus on meningitis, HPV, RSV, maternal/child health or healthy living, are in favour of vaccination, and had English speaking capacity (as the workshop was conducted in English).

A pre-read exercise was sent to participants two weeks before the workshop to equip them with a baseline level of understanding of IC and to introduce the four workshop themes. The exercise included an example patient information sheet for an RSV vaccine trial, alongside a 10 point questionnaire that was designed to test participant's comprehension of the document and provide an opportunity for them to generate thoughts on the topic being explored.

During the workshop, Nominal Group Technique (NGT) was used to explore issues that were considered pertinent within each of the four themes, and to reach consensus in terms of their significance. NGT follows a highly structured, face to face technique, and empowers participants by providing an equal opportunity to have their voices heard and opinions considered, whilst minimising researcher-bias.

Main Findings: The patient group representatives identified many issues surrounding the IC process, most of which fell under one of three major barriers:

A lack of a clear case for participation: Patient group representatives felt that IC documents should connect with patients, presenting a clear case for participation and offering a compelling story that is relevant and meaningful. The absence of a 'patient story' in IC documents was

considered a significant barrier to participation. Moreover, inclusion of excessive risk information was felt to contribute to the inability of IC documents to connect with patients, in that this information was perceived to be for the benefit of the sponsor (reducing their liability) rather than the patient. On the converse equipping participants with an understanding of the disease that a vaccine might offer protection against was considered motivating.

Difficulties with trust and relationship: The importance of communication, trust, and the relationship between researcher and patient emerged in nearly all of the nominal groups. For the participants, trustworthy and clear information was considered key, not only in the consent document but also in communication between researcher and patient.

The order in which information is presented is also important in establishing patient trust, with participants agreeing that it would be helpful to include a statement about ethical approval at the beginning of the document to show that the trial had been scrutinised by independent authorities and could therefore be trusted.

Communication not appropriately tailored: Long, complicated documents, technical/legal language and medical jargon were considered barriers to comprehension.

In children's assent, the scenario in which parent and child agree, and the child, parent and researcher work together was considered ideal, but family dynamics and hierarchy were acknowledged as potential barriers. For trials relating to sexually transmitted diseases it was felt that teenagers and parents should be able to have individual, private conversations with the researcher. Tailoring communications to the child's age and ability and testing comprehension were considered important and it was felt digital media could be helpful.

Participants acknowledged that while some gender-based communication differences do exist, they are not categorical. Therefore, participants were uncomfortable about the risk of making generalisations about gendered behaviours to inform the consent process. They suggested that communication should instead focus on connecting with and responding to the needs of patients.

2. Table of main results

Reference	Short description	Reference page
1	IC documents should be written with the patient in mind, presenting a clear case for participation through use of a compelling patient story.	p.30, p.31, p.32
2	Information on risks and benefits should be presented in a more balanced way. The inclusion of excessive risk information in current IC documents was perceived to be due to the sponsor's desire to limit their legal liability.	p.30, p.31, p.32
3	Protection from disease was a top motivating factor for participation in a vaccine trial. Participants felt the IC document should enable a better understanding of the disease that a vaccine might offer protection against, and any evidence of vaccine efficacy.	p.35, p.37, p.38
4	Communication and trust emerged as a key theme. Trustworthy and clear information was considered essential, within both the consent document and in the relationship between researcher and patient.	p.34, p.35, p.37, p.45, p.48, p.49
5	IC documents are frequently too long, incorporating technical/legal language and medical jargon which is difficult to understand. A short lay summary or flowchart at the beginning of the IC document would help facilitate understanding.	p.31, p.33
6	The order of IC documents needs to be considered. For example, sponsor information is off putting for participants and should be included later on in the document. Ethical approval was perceived to build trust and should appear near the beginning of the IC document to demonstrate that the trial had been independently scrutinised.	p.31, p.33
7	Negative perceptions of vaccines and the influence of anti-vaccine lobbyists are key influencers against taking part in a vaccine trial. These issues are societal factors and likely beyond the influence of the IC process.	p.36, p.39, p.40, p.41
8	Within assent, the ideal scenario is one in which parent and child agree, and the child, parent and researcher work together. However, family dynamics and hierarchies could be a barrier in a situation in which either a child wants to take part, but their parent/carer disagrees, or when the child is pressured into a decision by the parents/carer.	p.43, p.44
9	Participants suggested that comprehension tests should be carried out for children. Interestingly, this point was only discussed in detail during the assent theme, suggesting that participants felt a greater obligation to protect children.	p.42, p.43

10	IC communications should be tailored to respect the age and ability of the child so the child understands why they are being asked to take part and why the trial is important.	p.45
11	Digital tools were briefly discussed under the comprehension theme, although the topic of social media only fully emerged within the assent theme suggesting participants understood there to be a greater potential for the role of social media with younger audiences.	p.33, p.45
12	Participants noted situations in which gender may impact on the patient/researcher relationship, such as in trials relating to sexually transmitted diseases where individual, private conversations with the researcher should be available for both teenagers and their parents.	p.48. p.49
13	Although some gender-based communication differences were highlighted, participants felt strongly that gender stereotypes should be avoided within the IC process.	p.49

3. Background to the I-Consent project

The purpose of I-Consent is to improve the relationship between science and society, favouring informed engagement and dialogue with citizens and civil society within the area of research and innovation. The overall aim is to develop guidelines for the production of a comprehensive IC process. Dissemination of the results and contact with regulatory bodies may also contribute to the implementation of the results into the Good Clinical Practice guidelines.

The I-Consent project is comprised of six work packages (WPs). Work Package 1 establishes baseline knowledge on the issues concerning the IC process. It uses systematic review, supplemented with qualitative studies conducted with experts, to identify the challenges faced during the IC process. This task (1.6), within WP1, explores the patient group perspective and involvement in vaccine research by identifying issues relating to informed consent for vaccine trials in the areas of meningitis, cervical cancer and respiratory syncytial virus (RSV) vaccination in pregnancy. Specifically, participants were asked to consider the informed consent process in relation to:

- Comprehension
- Children's assent
- Impact of gender in vaccine clinical trials
- Patient expectations

Patient groups are organisations which represent and advocate on behalf of their patients. They play a unique role as passionate advocates for the prevention and treatment of the diseases they focus on. They are also intent on ensuring that the voices of those patients they represent are heard and taken into account. In line with this approach, a key requirement for achieving the objectives of the WHO European Vaccine Action Plan (2014, p. 45) is to "*Engage, enable and support in-country professional associations and societies, academic institutions and civil society organizations, to advocate the value of vaccines to communities, policy-makers and the media.*"

4. Introduction

The autonomy of an individual deciding to participate in clinical research is of major importance. Historically, the participation of individuals in clinical research has not always been voluntary. However, informed consent is now considered fundamental within clinical research and is described as, *"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate"* (ICH, 1996: p. 5).

The current IC process has been shaped through the implementation of international and national guidelines developed over the last 70 years. Notably, the Declaration of Helsinki (WMA, V1 1964) and the CIOMS Guidelines (V1 1982) established a framework for obtaining informed consent in clinical research. Subsequently, the Guideline for Good Clinical Practice (ICH, 1996) defined an international standard for quality within clinical research involving human subjects and has now been transposed into law in many countries. The ICH guidelines ensure that clinical trials must abide by strict ethical values, protecting research participants under the principles set out by the Declaration of Helsinki.

The process of informed consent has both ethical obligations and legal implications. It provides essential information about a clinical trial to potential participants and empowers them to make a rational and informed decision about participation. This typically occurs in two ways; verbally with the clinical researcher and by providing the individual with detailed documentation for them to read. The latter will typically take the form of an information sheet or booklet, aiming to describe the study in simple language, using non-technical terms and referencing the risks and benefits of participation.

4.1. Comprehension

Although informed consent is an essential principle in clinical research, issues related to comprehension by research participants have become evident. The informed consent documentation used for clinical trials has become highly regulated and legalistic as it also forms a contract between the industry, investigator and the participant. This has led to the introduction of longer and more complicated consent documents with participants often having a limited understanding of study information even when they have signed a consent form (Grady C, 2015).

4.2. Children and assent

Clinical research involving children and young people has traditionally been seen as laden with both ethical and practical challenges (Leibson and Koren, 2015). The Council of Europe's

Convention on Human Rights and Biomedicine (1997) categorises children as a vulnerable population and states that any persons, such as children, incapable of giving legal consent to clinical trials should be given special protection by the law. They may not be allowed to participate in clinical trials if the same results can be obtained from adults.

However, as children are physiologically and psychologically different to adults, age related research is important to ensure that medicinal products for children are tested scientifically before widespread use. Advocacy for the involvement of children in research is supported within international (The Clinical Trials Directive, 2001) and national (Nuffield Council on Bioethics, 2015) guidelines which warn that without research conducted in age-appropriate groups, there is a risk that children could be harmed by medicines that have only been tested on adults. In vaccine research, the participation of children is even more important since many vaccines are aimed exclusively at minors.

Whilst competent children could be considered to have the capacity to understand a study, in many countries, children entering clinical trials of medicines cannot legally give informed consent for themselves. Article 6 of the Council of Europe Convention on Human Rights and Biomedicine (1997) sets out that "*Where, according to law, a minor does not have the capacity to consent to an intervention… the intervention may only be carried out with the authorisation of his/her representative or an authority or a person or body provided for by law."* This gives rise to the problem of how to include children in the research consent process.

Assent is crucial to the participation of children in clinical research. It is defined as the willingness to participate in research by persons who are too young to give informed consent but who are old enough to understand the study, its expected risks and possible benefits, and the activities expected of them as subjects. The laws and ethical guidelines governing enrolment of children in clinical trials vary among countries (see Figure 1 for a summary covering participating patient groups' countries). For example, the Nuffield Council on Bioethics (2015) recommends that where children have sufficient understanding but are not legally able to give informed consent under the law of their country researchers should, wherever possible, seek consent from both children and their parents.

Figure 1: Ages for informed consent and requirements for children's assent in participating patient groups' countries

Country	Legal age of consent	Age for giving assent	Number of required signatories
Italy	18 years	Case-by-case assessment	Both parents
Netherlands	16 years	12-15 years with own signature	Both parents
Republic of Ireland	16 years (for clinical trials), 18 years (for all other research)	Assent can be given from 7 years, or according to the capacity of the child	One parent
Spain	16 years (informed consent to refuse medical treatment)	12-15 years with own signature	One parent
United Kingdom	16 years	Assent is not explicitly required. The explicit wish of a minor capable to form an opinion is considered by researcher	One parent

4.3. Gender in vaccine clinical trials

Gender is commonly used as a synonym for sex (Diamond, 2002). Yet the two are distinct concepts that should not be conflated. Whilst sex describes the purely physiological characteristics of males and females, gender encompasses the sociocultural qualities that help shape 'masculine' and 'feminine' behaviours (Guidance on Gender Equality in Horizon 2020).

Historically, theories on gender differences for communication were stereotypical. For example, the deficit model, first developed in 1922 describes women's language as being deficient to that of men's which was considered the norm (Hidalgo-Tenorio, 2016). The notion that women are vulnerable or inferior to men, has now been superseded with the view that men and women are heterogeneous groups, of which internal differences between them can be much greater than gender differences alone (Cameron, 2006; Hidalgo-Tenorio 2016). Indeed this perspective is the cornerstone of the diversity paradigm which suggests that gendered behaviour is influenced by many dimensions including age, class, ethnicity, social roles as well as religious and political beliefs (Cameron, 2006).

Independently of its format, informed consent is a communicative act. It is therefore important to consider differences in communication by gender, to enable the development of audience appropriate informed consent. Yet, to our knowledge, there are no guidelines on how to adapt the IC process by gender, although there is some evidence that men and women express different preferences in the way in which informed consent is presented (Knepp, 2014). Where guidelines are in place, they tend to reference safety concerns relating to pregnant or breastfeeding women or those of childbearing potential which recommend that researchers

need to exercise special care with female participants in certain social, cultural or physiological situations. As the CIOMS guidelines (V4 2016, p. 58) states, "*Pregnant women must not be considered vulnerable simply because they are pregnant*", however, *"specific circumstances, such as risks to the foetus, may require special protection".*

In the context of vaccine trials, gender deserves consideration given that women are often the specific targets. For example, in Europe, adolescent girls are deemed the priority target for preventing cervical cancer via Human Papilloma Virus (HPV) vaccination, and the platform for vaccination in pregnant women is ever growing, currently including flu and pertussis, and with RSV and Group B Streptococcal vaccinations currently in development. Moreover, the consensus amongst experts is that parental authorisation for the participation of infants and children in vaccine trials is almost always given by the mother (personal communication with investigators at leading UK vaccine trial institutions).

4.4. Patient expectations

Patients' expectations of clinical trials also need to be considered from an ethical perspective. Subjects may harbour misconceptions about the research and the burden of participation may affect enrolment and retention levels (Frisaldi et al, 2017). In addition, patients may like to know how they contributed to outcomes of the research, and may therefore have expectations regarding personal feedback about the research results. Fully understanding the implications of patient expectations will elucidate factors which ultimately affect recruitment and retention.

Trials of therapeutic agents may have high associated risks. However, for those patients suffering from an incurable illness any potential benefits of the treatment, from relief of symptoms to lengthened life expectancy, may outweigh such risks. This could be a significant incentive to participate in a therapeutic clinical trial.

In contrast, the target population for vaccines are healthy people, including children. As a result the general public have a low tolerance to any adverse events following vaccinations (Kulkarni, 2013). While the individual risks from vaccine trials are often relatively low, the individual benefits are also likely to be lower. Current vaccine research focuses on diseases which are either very severe but rare, or relatively mild but common, as the majority of common and lethal or universally disabling diseases are already vaccinated against.

There may be limited personal benefit to participating in some vaccine trials, meaning key motivating factors may be more altruistic, such as achieving benefit for the health and well-being of society, should the research be successful. Indeed a recent review of barriers and motivations for participation in vaccine trials (Detoc, 2017) found that altruism was the most cited motivation for participation in vaccine trials, and it has also been reported as an important

motivating factor for engaging in clinical research amongst chronic disease patients (DasMahapatra, et al, 2017).

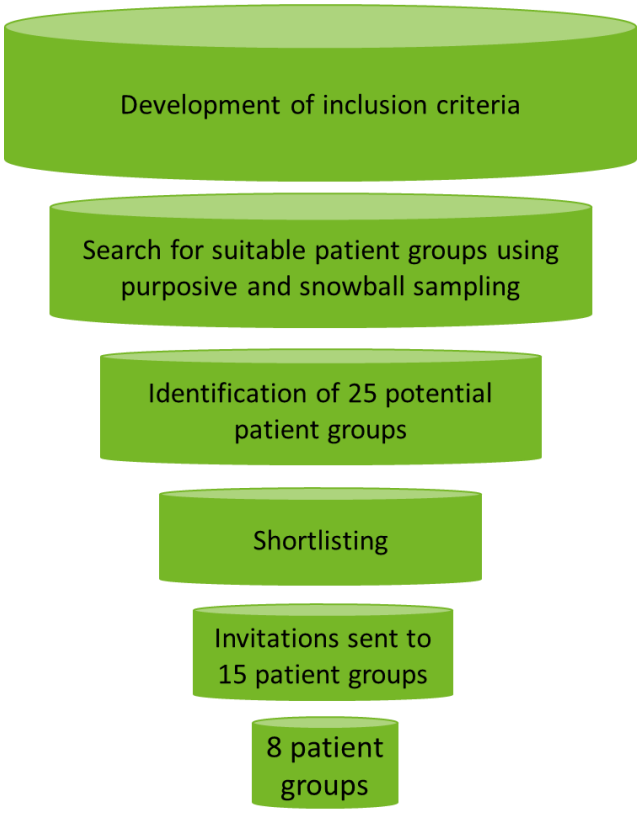
Tied within expectation is compensation. Compensation is typically paid to trial participants for reasons such as relieving participants of financial sacrifice, as an appreciation of their contribution to medical science or for achieving recruitment where the target population is difficult to reach (Pandya and Desai, 2013). Financial inducement is considered ethically unacceptable as it may cloud the potential participants' appreciation of any risks, reducing the likelihood that consent is genuinely informed (Grady, 2015). As a result, any financial rewards must be limited to compensation for travel, time and inconvenience. However, the modest compensation received by patients could be perceived as undervaluing the contribution they have made to global health (Sheehy and Meyer, 2012). Therefore, this is an ongoing issue and one which has not been fully investigated.

5. Design of Task 1.6

5.1. Selection of patient groups

Nine participants from eight patient groups, based in five European countries, were recruited to attend a one-day workshop located in central London.

Figure 2: The process for selection of patient groups



The criteria for selecting and shortlisting patient groups was as follows:

- Directly represents patients
- Focuses on meningitis, HPV, RSV or healthy living
- Advocates for vaccination
- An active organisation
- Has English speaking capacity

Anti-vaccine groups and patient groups focused on genetic conditions (with the exception of diseases that result in an increased susceptibility to HPV, meningitis and RSV) were excluded on the basis that either their motivations would not be in line with the overall workshop aims or they were focused on conditions for which vaccines are not available.

Suitable patient groups were identified using a combination of purposive sampling and snowball sampling. In order to streamline the recruitment process, and to minimise the risk of participants dropping out of the project, groups known to Meningitis Research Foundation (MRF) were prioritised. This included I-Consent consortium partners and umbrella organisations which MRF are members of, such as the Confederation of Meningitis Organisations (CoMO) and the Association of Medical Research Charities (AMRC). Additional patient groups were identified through targeted searches of electronic databases and resources.

An initial search identified 25 potential patient groups for inclusion in the workshop, however following a shortlisting procedure, which involved comparing the relevance of the organisation to our pre-determined inclusion criteria, 10 were excluded due to a lack of relevant expertise, or because they no longer appeared to be active in their field. The remaining 15 patient groups were invited to the workshop via e-mail (invitation email template in Annex 1). The email was personalised to each recipient and tailored to the focus of the organisation. If there was no response, invitation emails were followed up with a further email and / or telephone call. From the invitations sent, eight patient groups accepted, three declined (due to limited capacity), and four failed to respond.

5.2. Profile of participants

The eight patient groups that attended the workshop are shown in Table 1. As can be seen from the table the participants had expertise in a variety of fields, however, meningitis was the focus of three out of the eight organisations.

Many of the workshop participants occupy senior positions within their organisation and a number are founding members. Despite a high level of expertise within their area of focus, prior knowledge of clinical trials and the IC process varied across the group with few having direct experience of the topic.

As we did not have direct access to patients, we relied on the patient groups having insight into the perspectives of their patients and being able to successfully represent these perspectives during the workshop. Some workshop participants gave examples directly referencing their area of expertise, whilst others spoke of issues in a general sense. The impact of this was positive and led to the generation of a wide range of ideas.

Table 1: Description of patient group participants

Representative's role	Gender	Country	Organisational focus
Research and Information	Female	United Kingdom	Raising awareness of meningitis to enable prompt diagnosis, funding research and providing support to people living with the impact of meningitis.
Leadership	Female Male	Italy	Welfare of parents and families
Leadership	Female	Spain	To provide information about meningitis symptoms, to raise awareness and promote vaccinations throughout Spain
Leadership	Female	United Kingdom	Working to stop Group B Streptococcal infections in babies.
Content and Information	Female	United Kingdom	Support for babies born premature or sick.
Leadership	Female	The Netherlands	Supporting families who have experienced meningitis, encephalitis and septicaemia.
Communication and technology	Male	Republic of Ireland	Promotes gender equity in public health, research and social policies across Europe.
Leadership	Female	The Netherlands	Advocates for the best care and quality of life for people with a liver disease.

5.3. Pre-read exercise

A pre-read exercise (Annex 2) was created in order to equip attendees with a basic understanding of informed consent and to introduce the four themes to be discussed at the workshop. The pre-read consisted of 17 slides, and was e-mailed to participants approximately two weeks before the workshop, with the advice that it would take around an hour to complete.

The opening slides provided a short introduction to the aims and objectives of the I-Consent project as a whole, as well as outlining the specific aims of the workshop. This was followed by an introduction to the concept of informed consent, and its importance in research, the description of which was supported through use of a video excerpt. The final part of the introduction underlined the need for an improved IC process due to shortcomings in the current approach, and the importance of participants' perspectives.

After providing participants with a basic understanding of the IC process, the pre-read introduced the four themes to be discussed at the workshop. For each theme, there was at least one explanation slide providing background information, and explaining the theme's importance in relation to vaccine trials. For the assent theme, a map indicated the legal age of consent for research in our participants' countries. Each theme also included a slide setting out

the workshop question formulated to explore that theme, with an illustration (see example in Figure 3) to provoke the participant to start thinking of issues.

Figure 3: Illustration used to encourage participants to generate issues on the topic of children's assent

Finally, participants were provided with a real life example of a patient information document, and asked to answer a 10 point questionnaire (set up using Survey Monkey). The questionnaire was designed to test participant's comprehension of the document and provided an opportunity for them to generate thoughts on the topic being explored. Results from the survey were analysed and presented during the workshop to open discussion on the issue of comprehension.

The patient information sheet chosen was '*Developing a vaccine to prevent RSV, a cause of serious respiratory infections in infants'* (Annex 3). It was 14 pages in length and contained some technical jargon, for example referring to the trial vaccine as *'Ad26.RSV.preF.'* Before selecting this example we looked at more than 12 patient information documents for vaccine trials. These were collected from the websites of four UK institutions responsible for running vaccine trials, and personal contact with individuals working at Oxford Vaccine Group, St George's Vaccine Institute, and Bristol Children's Vaccine Centre. This example was selected because it enabled exploration of three of the four workshop themes: comprehension (an example of a technically complex, lengthy document typical of IC documents used today), assent (the trial

was recruiting children) and patient expectation (through asking participants what they anticipated their involvement would entail).

5.4. Workshop methodology

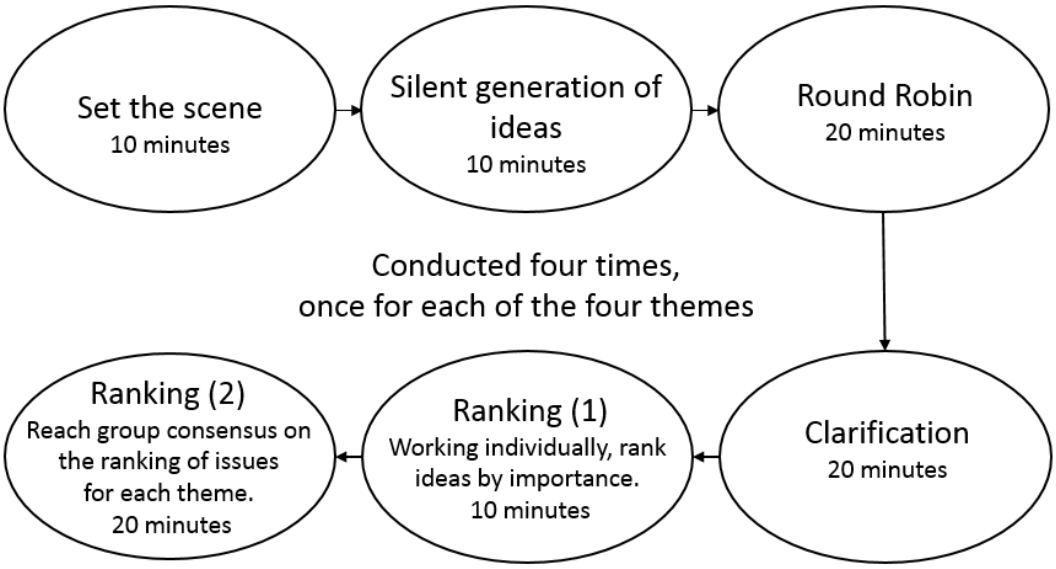
The objective of the workshop was to explore and document issues within informed consent for clinical vaccine trials from the perspective of patient groups, with a focus on the following themes:

- Comprehension
- Children's assent
- Gender
- Patient expectations

Nominal Group Technique (NGT) was employed during group exercises to explore the issues pertinent within each theme and to reach a consensus in terms of their significance. Originally designed by Van de Ven and Delbecq (1974), NGT is a well-established method in social research, which allows consensus to be reached in a group setting. It follows a highly structured, face to face technique as shown within Figure 4, which empowers participants by providing an equal opportunity to have their voices heard and opinions considered by other members, whilst also minimising the researcher-bias. An additional benefit of the NGT approach is that there are no negative impacts if the workshop organisers and participants are already known to each other. This enabled the recruitment of some groups who MRF already had existing relationships with.

The NGT compares favourably with other group processes such as Delphi (Okoli and Pawlowski, 2004), focus groups (Stewart and Shamdasani, 2015) and brainstorming, as minimal preparation is required by participants prior to the workshop, participants' input is limited to a single meeting, and the structure prevents more vocal participants from dominating the discussion.

Figure 4: Overview of the Nominal Group Technique process



The group exercises in this workshop followed the NGT structure set out below:

1) Assemble the group

After brief introductions, the workshop began with an overview of the project and its purpose, reinforcing the value of each participant's contribution.

2) Scene setting stage

Before commencing each nominal group, the facilitator presented a short introduction to the theme using a slide presentation prepared by the organisers. For each theme, a video was used to set the scene, except for the gender theme for which storyboards were used as no suitable video could be identified.

3) Silent generation stage

Each participant was given sticky notes and instructed to write down as many individual issues as possible in response to the nominal group question, using a separate sticky note for each idea. There was no limit to the number of ideas the participants could generate. This stage was conducted in silence and repeated for each of the four themes.

4) Round robin stage

Participants were then instructed to take it in turns to read out one of their ideas and pass the note to either the facilitator or one of the workshop organisers who placed the sticky note on the whiteboard. However, in the latter two sessions, some participants self-moderated their ideas, removing duplicates before they had been handed over to the workshop facilitator / organiser. They also began to read out their sticky notes in a random order and took some time to explain the reasoning behind their idea. The latter occurred because although the workshop was conducted in English, for over half the group English was not their first-language. Therefore there was some overlap between the round robin and clarification stages.

Participants were able to continue recording and offering new ideas during the round robin process, but were instructed to wait their turn before sharing them with the group. This process continued until no new ideas were forthcoming. This stage was repeated for each of the four workshop themes.

5) Clarification stage

The workshop facilitator went through each idea on the whiteboard to ensure participant understanding, seeking clarification where required. With the agreement of the participants, similar ideas were grouped and participants were asked to think of an appropriate name for the grouped issues, which are referred to henceforth as 'sub-themes'. This stage was repeated for each of the four workshop themes.

6) Ranking stage

The ranking stage was split into two parts:

1) A numbered ranking sheet (Annex 4) was given to each participant and they were asked to rank the sub-themes in order of importance. They did this by scoring the sub-theme they found least important as 1, and so on up to the most important, so that if there were nine sub-themes, the maximum score would be nine. Participants were asked to do this separately without conferring. One organiser quality-checked the ranking sheets as they were handed in, for example to ensure that participant's had only used each number once in their scoring.

2) During the breaks, the organisers entered the scores from each individual ranking sheet into a spreadsheet and added them together to calculate the total scores for each sub-theme. This stage was repeated for each of the four workshop themes, producing a prioritised list of sub-themes for each theme. We had intended to present back the prioritised list to the group for discussion after each nominal group and before moving onto the next, providing an opportunity to alter the order of

priorities while the topic was still fresh in the minds of participants. However, due to time constraints all the combined scores were presented at the end of the workshop, except for the comprehension theme which was discussed as soon as the priorities had been calculated.

The workshop was scheduled according to the timings recommended for each stage of NGT by McMillian, King and Tully (2016), as shown in Figure 4. Extra time was allocated to the theme of comprehension as it was the first nominal group conducted that day and participants needed to get used to the format. Extra time was also allocated to present the pre-read survey findings as an introduction to the comprehension section (see Annex 5 for the workshop agenda).

In practice, the earlier sessions took longer than anticipated and there are a number of possible reasons for this:

- It took some time for participants and organisers to get used to the exercise and the first two sessions involved additional steps, described in the 'Workshop findings' section below.
- Participants had more energy at the start of the day and were more forthcoming with ideas. The volume of ideas generated was higher for the first three themes: 52 for comprehension, 55 for patient expectations, 51 for child assent compared with gender for which only 30 ideas were generated.
- The topics discussed earlier in the day (comprehension and patient expectations) were easier to understand and engage with.

5.5. Data management

During the workshop, we used a spread sheet on Microsoft Excel 2013 to record the scores given by individual participants and to calculate the combined scores. This provided a list of priorities which were presented back to the group at the end of the workshop, or for comprehension, at the end of discussion around the theme. This allowed us to generate the combined scores very quickly and to feedback to the participants during the workshop.

5.6. Data collection

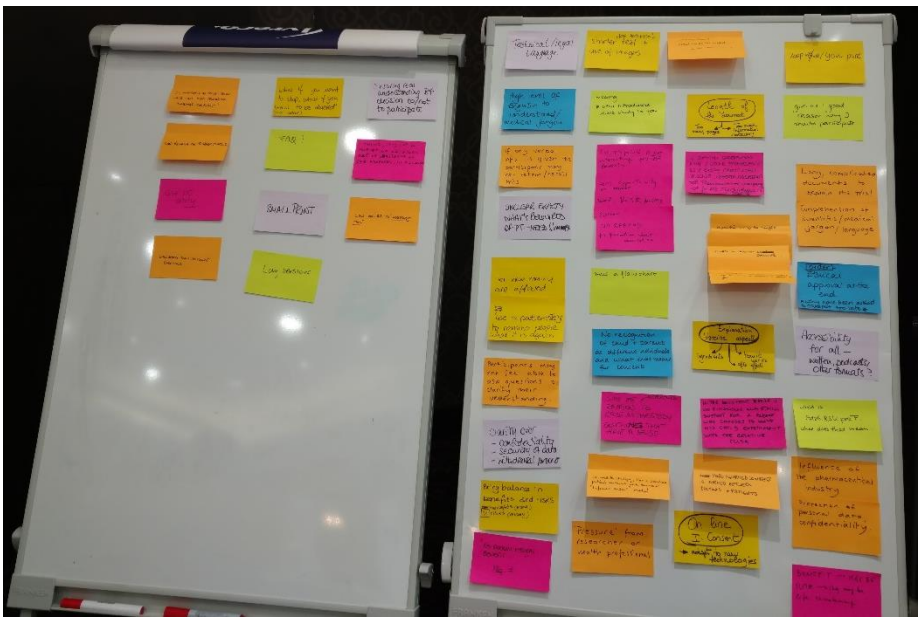
The workshop was voice-recorded in its entirety and written consent for the digital audio recordings was obtained from the participants prior to the workshop, with the exception of two participants who wanted to take part but not to be recorded. Ahead of the workshop, the two participants agreed they would relay their ideas to the workshop facilitator who would then state them aloud to the group. This allowed their ideas to be recorded and ensured that their input would not be missed during the analysis stage.

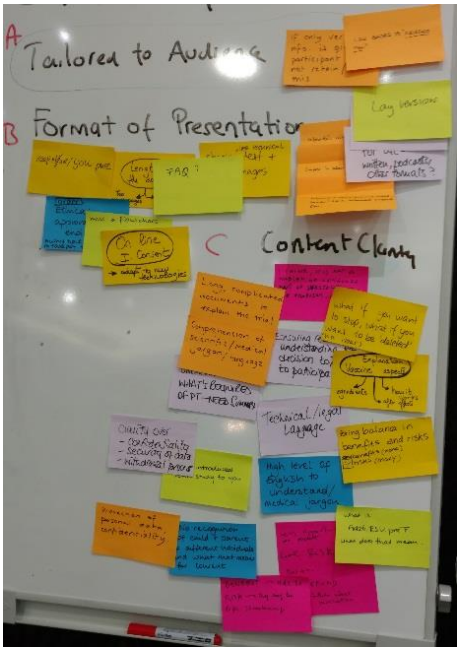
The recordings from the round robin, clarification and ranking stages of each nominal group were transcribed in-house. The purpose of this was to enable the researchers to review the transcripts during analysis to ensure the original meaning of the ideas generated were interpreted correctly.

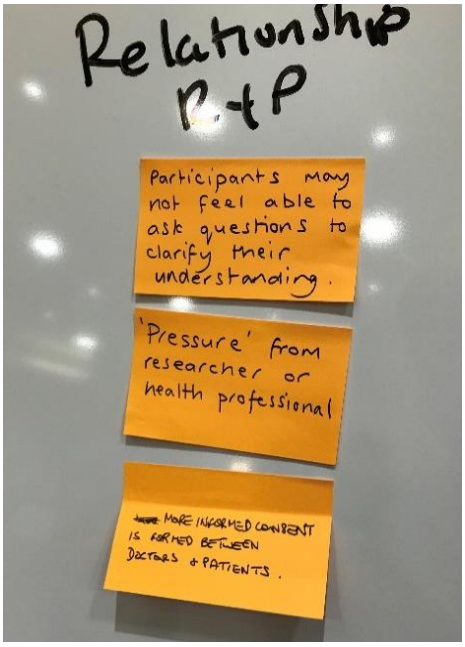
Four workshop organisers were also present and took notes throughout the day. They focused on documenting the key interactions between patient groups and the main discussion points identified, as well as being available to answer questions about the process or topic.

The raw materials generated at the workshop (i.e. the sticky notes and ranking sheets) were collected and written up by the workshop organisers after the workshop was concluded (Annex 6 - 9). Photographs (shown in Figure 5) were also taken of the boards with all of the grouped sticky notes at the end of each clarification stage to document the round robin and issues clarification steps for each nominal group.

Figure 5: Photographs of the sticky notes generated during the silent generation and round robin stage, and their grouping following the clarification stage.




A Tailored to Audience
B Format of Presentation
C Content Clarity
FAQ
Lay Versions
Technical/legal Language


Relationship P-t-P
Participants may not feel able to ask questions to clarify their understanding.
'Pressure' from researcher or health professional
MORE INFORMED CONSENT IS FORMED BETWEEN DOCTORS & PATIENTS.

6. Workshop findings

In this section we use three terms to convey a specific meaning:

- *Themes* are the four topics discussed in each of the four nominal groups: comprehension, patient expectations, assent and gender.
- *Issues* are the ideas generated by the participants during the silent generation and round robin stages of each nominal group, and written and displayed on sticky notes. These issues were clarified in discussion, duplicate issues removed, similar issues grouped and these clarified issues expressed as sub-themes.
- *Sub-themes* were then ranked in order of importance by participants at the end of each nominal group session.

During the workshop there were a number of deviations from the methodology described in Section 5.4. Firstly, participants explained their ideas during the round robin stage which lead to an overlap between the round robin and clarification stages. This, however, was beneficial in facilitating discussion as it encouraged the involvement of non-native English language speakers by providing them with additional time to explain their ideas.

Secondly, after the combined ranking scores for the first theme (the comprehension theme) had been presented back to participants, time restrictions meant that the combined scores for the final three themes were presented at the end of the workshop rather than immediately after each nominal group. Although there was some discussion about sub-themes lower down on the priority list being of equal importance, participants did not suggest re-ordering the priorities of sub-themes in any of the nominal groups. Despite these deviations, the workshop progressed well and it is not expected that these events had a substantial impact on the quality or quantity of the information obtained.

6.1. Theme 1: Comprehension

What features of the informed consent process may make it difficult to understand?

Comprehension was the first theme discussed during the workshop, and instead of using a scene-setter it was introduced by presenting the questionnaire results from the pre-read which both tested and surveyed opinion on comprehension in informed consent.

6.1.1. Pre-read survey results

After reading the example informed consent form (Annex 3), participants had been asked to complete a 10-point questionnaire (Annex 10), which consisted of three questions designed to

test comprehension, and seven questions to survey participant's views and opinions of the IC document. Eight participants from nine different patient groups completed the questionnaire, as one patient group had two representatives who decided to complete the questionnaire together (Table 2).

Table 2: Participants' responses to the pre-read questionnaire. Correct answers to the first three questions, which test participants' comprehension of the IC document, are shown in green font.

Question	**Answers**	***n***
Q1. Throughout the course of the trial, how many routine home visits will the participant receive from the nurse or doctor in total?	7-9 visits over a 30-week period	5
	7-9 visits over a 52 week period	1
	5-7 visits over a 52 week period	1
	Don't know	1
Q2. What has been done to the Adenovirus used in this AD26.RSV.PreF vaccine to stop it causing colds and respiratory infections when the vaccine is injected?	It has been weakened so that it cannot multiply	5
	It has been killed so it cannot cause disease	0
	It has been modified so it cannot use the human body's genes to make proteins	0
	It has been transformed into an inactive form of the RSV virus	0
	Don't know	3
Q3. Will participants be able to find out whether they received the vaccine or the placebo?	Yes – after the end of the trial	3
	Yes - anytime throughout the trial	1
	No	3
	Don't know	1
Q4. After reading the informed consent document could you make an informed decision on participation?	Yes	7
	No	1
Q5. On a scale of 1 to 5, how helpful was the document in enabling you to understand what disease this vaccine might provide protection against?	5	2
	4	4
	2	2
Q6. Page 6 explains the potential side effects that may be experienced when taking part in this trial. On a scale of 1 to 5, overall how helpful was this?	5	1
	4	5
	2	2
Q7. Would you know who to contact if your child suffered a mild adverse reaction?	Yes	7
	No	1
Q8. Page 10 provides information about the confidentiality of data collected in the study. On a scale of 1 to 5, how easy or difficult did you find this information to understand? (5=very easy, 1=very difficult)	5	2
	4	0
	3	3
	2	3
	1	0
Q9. If you met the recruitment criteria, how likely is it that you would enrol your child in this trial? 5= very likely 1= very unlikely	5	0
	4	2
	3	3
	2	3
	1	0

Participants' opinions of the informed consent document

Overall, participant's views of the IC document as reported in the survey were positive. Nearly all (7/8) participants felt they would be able to make an informed decision on whether to participate. The majority of participants (6/8) found the IC document either helpful or very helpful in understanding what disease the vaccine is designed to protect against, and 6/8 also found the document either helpful or very helpful in explaining the potential side effects for children taking part in the trial. Additionally, nearly all (7/8) participants responded that they would know who to contact if their child suffered a mild adverse reaction.

Participants' opinions of the information provided in the IC document about the confidentiality procedures for data collected were more neutral or negative: only 2/8 rated it as very easy to understand, 3/8 were neutral, and 3/8 found that it was very difficult to understand.

Despite expressing positive views about how well the IC document explained the disease the vaccine is designed to prevent and the potential side effects, only 2/8 participants answered that it was likely they would enrol their child in the trial, with the remainder of participants evenly spread between neutral and negative.

Participants were also given the opportunity to provide any additional comments about the consent form and only three participants provided comments, which in summary described the information booklet as *'very wordy'* and *'too long and very technical.'*

Comprehension testing

Although nearly all participants felt the IC document enabled them to make an informed decision on whether to take part in the trial, and most respondents found explanations in the IC document helpful, the comprehension test showed that comprehension was far from perfect. In fact, none of the comprehension questions were correctly answered by all participants.

Participants had the most difficulty understanding whether or not those involved in the trial could find out whether they had received the vaccine or placebo, with only 3/8 correctly answering that they would be able to find out after the end of the trial. Most (5/8) participants correctly answered the question about how the adenovirus had been modified to stop it causing disease, and most (5/8) correctly answered how many routine home visits were involved in the course of the trial.

Overall, the participants who spoke English as their first language answered more questions correctly than those whose first language was not English. Of the four native English speakers,

two answered all the questions correctly, one answered two out of the three questions correctly, and one answered *'Don't know'* to all three questions. In comparison, of the four questionnaires completed by non-native English speakers, one correctly answered two questions and three correctly answered one question. Therefore, amongst this small cohort of participants, although having a better command of English was an advantage, comprehension was still imperfect amongst the native English speaking contingent of this highly educated and professional group of participants.

Discussion of pre-read at the workshop

Despite the respondents rating the consent form positively in their surveys, a contrary perspective emerged during the workshop discussion of the pre-read, with many participants criticising the length and complexity of the document. One participant said; '*Really long, complex, even as being someone use to reading them [informed consent documents] it just wasn't accessible – not a handy summary to let you know what you need to know.'* One participant explained that difficulty understanding the document was the reason they would have decided not to participate *'Agree, - so I answered unlikely to let my child participate because of the quality of the document – too long…'*

During discussions one participant specifically made reference to the influence of the pharmaceutical companies as being off putting; *'First page I thought [I'd] take part…but then I read it's from a pharmaceutical company so it's all about money so it put me off. So maybe it's not very good to put that at the first and there's so much information as they are just protecting themselves – not very inviting to take part!*' This negative perception towards the influence of the trial sponsor is discussed in a greater detail in the next section.

6.1.2. Workshop findings: comprehension

Overview of findings

In the round robin stage the nine workshop participants collectively generated 52 ideas which were written on individual post it notes during the silent generation stage. During the clarification stage, these ideas were grouped into nine sub-themes which are listed in the table below. From this we can see that the sub-themes with the highest scores generated the largest number of individual issues, produced during the silent generation phase. This suggests that even when working alone, participants considered similar issues relevant to comprehension in informed consent, and, if volume of ideas generated is an indicator of the importance of a topic, they may have had similar views on which issues were most important even before feeding back and discussing as a group.

Table 3 lists the nine sub-themes in order of importance as prioritised by participants. Scores for each sub theme were added together, and for each sub-theme the total score is shown, along with the median, mean and standard deviation, as well as the number of individual issues that were generated under each sub-theme. '*Why should I take part',* received the highest total score: 65 points out of a possible 81 and an average score of 7.2 (SD = 1.8). This was closely followed by '*content clarity'* which received a total of 63, and on average an individual score of 7 (SD=2.7). The third most important issue was '*format of presentation'*, receiving a total of 54, and on average an individual score of 6 (SD 1.8). The further six sub-themes included fewer individual issues, with lower scores that tended to bunch together, so consensus as to the exact priority of these further sub-themes may not have been as strong as for the first three.

Table 3: Comprehension: sub-themes shown in the order prioritised by participants. Participants awarded the highest possible score of 9 to the sub-theme they judged as the most important and the lowest score of 1 to the issue they judged least important.

Sub-themes	Total score (max = 81)	No. of individual issues	Median	Mean	Standard deviation
Why should I take part? *E.g. Patient story, proposal not interesting for parents, decisions may involve emotions.*	65	10	7	7.2	1.8
Content clarity *e.g. Explanation vaccine aspects - ingredients, how it works, after effects, balance of benefits and risks, many risks vs limited benefit', technical language, confidentiality of data and right to withdraw*	63	18	8	7	2.7
Format of presentation *e.g. small print, lay versions, shorter documents, structure*	54	13	7	6	1.8
Tailored to audience *e.g. law refers to average man*	47	2	5	5.2	2.4
Relationship researcher and participant *e.g. participants not feeling able to ask questions, pressure from health professionals*	47	3	5	5.2	2.3
Decision making *e.g. don't put all your hope in one document*	41	1	4	4.6	2.3
Model *e.g. IC process needs a better model*	39	2	4	4.3	2.4
Sponsor perception *e.g. influence of pharmaceutical industry*	27	2	3	3	1.7
Bias *e.g. how might internal biases influence perceptions of IC processs?*	22	1	2	2.4	2.2

Why should I take part?

'Why should I take part' and *'content clarity'* were considered to be of similar importance, which is consistent with the subsequent discussion in which it strongly emerged that participants felt that there needs to be a clear case for participating, involving a compelling patient story, and an appreciation of the emotional responses of patients/parents. In addition to this, it was felt that the content of the document needs to be clear, minimising medical jargon and clearly setting out the risks and benefits.

This focus on the importance of understanding the case for participation was also consistent with the discussions on the later theme of patient expectation (Section 6.2), in which understanding, as well as the protection/efficacy offered and disease awareness emerged as top motivators for taking part in a vaccine trial. Therefore it is unsurprising that without understanding what the benefits are, participants feel unmotivated to take part.

The influence of the sponsor was also discussed under the sub-theme of *'Why should I take part'*, with some participants suggesting that the example IC document seemed to have been written with the sponsor in mind as opposed to the patient. *'It's difficult to understand why she as a mother should participate in this study, it seems, from the documentation, important for the pharmaceutical company but not important for her...'* The perception that the document is designed to reduce the liability of the sponsor, conflicts with the primary objective of the IC document as a means of ensuring that a patient can make an informed decision on research participation (ICH, 1996). Indeed one participant even commented that the *'informed consent current model sounds like an insurance proposal.'* Since its conception, the IC document has undergone significant changes, in part due to the development of international guidelines established to provide ethical and regulatory standards for research conduct. However, due to these guidelines emphasising the importance of information disclosure, over time, attempts at transparency have resulted in the excessively lengthy and complex documents often used in research today.

Interestingly, the participants did create a sub-theme on sponsor perception, discussing the influence of the pharmaceutical industry. However, as a standalone sub-theme it was not perceived to be a major barrier to comprehension, receiving just 27 points out of a possible 81.

The results of the ranking and transcripts of the workshop discussion, demonstrate clear consensus from the group in that the greatest barrier to comprehension in the IC process is an inability of the document to connect with the patient. As a result, the group felt that patients are unable to appreciate the importance of the study, which in turn leads to a lack of engagement with the trial. This is captured through comments such as *'I missed the patient story,' 'Give me one good reason why I should participate. That's what people want to know,*

why should I get involved? What's the benefit for me or my child?' , 'Why do I need to involve my child in this… if it feels like it's something you can understand and relate to then you are more likely to engage'.

To our knowledge, this study is the first to reveal that from the patient perspective, the lack of an understandable case for participation and a compelling patient story, is the greatest barrier to comprehension - having a greater influence than clarity of content and format.

Content clarity

Under the sub-theme of *'content clarity'* a number of issues emerged, with participants most frequently criticising:

- Imbalance of risk vs benefits *'…benefits (none) risks (many)'*
- Language; inclusion of too much *'medical jargon'*
- Lack of clarity over *'confidentiality, security of personal data'* and the *'withdrawal process'*

The imbalance of information on risks and benefits emerged as a major barrier to patient comprehension; *'I missed the balance between the benefits (there are none) and the risks (there are many). There must be some benefits, but they aren't mentioned.'* With participants suggesting that a balanced view of risks and benefits is necessary to provide a compelling patient story. Nusbaum et al (2017) found that a group of experts shared concerns over the way in which risk information is communicated, particularly during the 'consent encounter' which refers to the interaction between the health professional and patient. However when these experts were asked how best to convey the probability of risks and benefits during these encounters, suggestions were diverse ranging from using precise numbers to verbal descriptions.

The inclusion of an extensive description of all possible risks, regardless of their probability, is opposed by recommendations from the US Food and Drug Administration (FDA, 2014) which suggests that*: "[…] All possible risks do not need to be described in detail in the informed consent form, especially if it could be overwhelming for subjects to read. Information on risks that are more likely to occur and those that are serious should be included".* The tendency in IC documents to include an exhaustive list of all possible risks no matter how remote from biological plausibility and undermining understanding of the study may also result from the sponsor's desire to limit their legal liability.

Format of presentation

Within this sub-theme, participants emphasised the length of the document *'Length of the document - too many pages, too much information unnecessary',* simplicity of language *'Information must be simple'*, as well as the desirability of digital format as an alternative to traditional written documents *'Online I-Consent - adapt to new technologies', 'Accessibility for all - written, podcasts/other formats?'.*

The importance of the structure of the IC document was emphasised both in issues offered during the round-robin *'Miss a flow chart', 'Lay version?', 'FAQ?', 'Order: ethical approval at the end.'* and in subsequent discussion.

Participants' consensus that the inclusion of a lay summary or flowchart at the beginning of the informed consent document would help facilitate understanding of what participation involves concurs with the new EU clinical trial regulation 536/2014 (Article 37) that mandates a *'summary of study results that is understandable to laypersons'* for all clinical trials conducted in the European Union. These layperson summaries will be accessible in a new EU database once it becomes available and is approved according to the timelines set forth in the regulation (European Commission, 2017).

Participants also felt that the inclusion of sponsor details at the beginning of the document was off-putting, and that not mentioning ethics approval until near the end was unhelpful. This issue re-emerged during discussions on the later theme of children's assent (see Section 6.3). One participant suggested that having ethical approval at the beginning of the document would be reassuring to prospective participants *'…to read on knowing it's been scrutinised, and it's not just a pharmaceutical company sending you this..'* This supports the view of Nystrand (1986) who suggests that the information at the beginning of a document forms the basis for a reader's interpretation of the rest of the information.

Given the volume of existing literature that suggests that the format, i.e. the length of the document and volume of information included (Lorell et al 2015; Pandiya 2010), is the major barrier in the IC process it is perhaps surprising that this sub-theme emerged a relatively distant third in priorities assigned by our participants.

Whilst our results do still highlight the importance of all these aspects of format, the content and the effectiveness of the IC document in connecting with the patient in a meaningful way was considered to be of greater value. This perhaps offers an explanation as to why attempts to improve comprehension through the use of shorter documents have often had little success. Indeed both Stunkel et al (2010), and Grady et al (2017) found that neither comprehension of study information nor satisfaction was affected by the length or complexity of the consent

form. Despite concise consent forms appearing to offer little benefit to the patient, it has been suggested that alternative benefits may include a reduction in the time that review committees spend on consent forms (Grady et al, 2017).

Relationship between researcher and patient

This sub-theme included three issues: *'more informed consent is formed between doctors and patients', 'participants may not feel able to ask questions to clarify their understanding'* and *'pressure from researcher or health professionals'*. It did not rank very highly in this nominal group, tying for 4th highest priority with the sub-theme *'tailored to audience'* however *'relationships'* also emerged in the subsequent *'patient expectation'* theme and ranked as the most encouraging factor for participation in vaccine trials (see Section 6.2).

6.2. Theme 2: Patient expectations

When deciding whether to take part in a vaccine trial, participants will have certain expectations. What might encourage them to take part and what might put them off?

During the round robin stage, 55 individual issues were generated by workshop participants under the theme of 'patient expectations'. These issues were then categorised into 16 sub-themes. We altered the standard procedure for this nominal group and decided to rank the sub-themes twice, firstly asking participants to consider what might encourage them to take part in a vaccine trial and the second time considering what might put them off. This decision was made during the workshop as the sub-theme titles generated by the group included inherently biased wording such as 'negative perception of vaccines'.

As before, participants were asked to give the issue perceived as the most important the highest score, descending to the issue they judged least important which would get the lowest scores. In this instance, as there were 16 sub-themes the highest priority issue would get an individual score of 16.

Although the decision to rank the sub-themes twice allowed for a more detailed understanding of the factors relating to patient expectations, due to a lack of time to prepare the amended ranking sheets and brief the participants accordingly, some participants had difficulty understanding the adapted ranking process. One participant misunderstood the scoring system and unfortunately the resultant scores could not be included within the analysis.

The overall scores show that the factors that encourage people to take part are not simply the reverse of those they consider off-putting. Therefore, certain factors are more powerful for encouragement than the converse would be as a discouragement and vice versa.

Some sub-themes, such as *'values/culture'* and *'media'*, were expressed in entirely neutral language, but in discussion and ranking participants seemed to perceive these sub-themes as more powerful as negative influencing factors than as positive influencing factors.

6.2.1. Factors encouraging participation in a vaccine trial

Table 4 lists the 16 sub-themes in order of importance as prioritised by participants in response to the question of what might encourage participation in a vaccine trial. Scores for each sub theme were added together, and for each sub-theme the total score is shown, along with the median, mean and standard deviation, as well as the number of individual issues that were generated under each sub-theme

The *'relationships and understanding'* sub-theme received the highest total score at 113 out of a possible of 128 and an average score of 14.1 (SD = 1. 9). There was strong consensus on the importance of this sub-theme as indicated by the score achieved and low standard deviation. *'protection/efficacy'* was collectively scored as the second most important issue with a total score of 100 and an average score of 12.5 (SD = 2.6). *'Disease awareness'* scored a combined total of 96 with an average score of 12 (SD = 4.0). In this case, the high standard deviation indicates that consensus within the group on the perceived importance of this sub-theme was not as strong as for the other sub-themes. '*Economic compensation'* achieved a score of 95 and an average score of 11.9 (SD = 2.5).

Table 4: Patient expectations: sub-themes are shown in the order prioritised by participants when considering what might encourage them to take part in a vaccine trial. Participants awarded the highest possible score of 16 to the sub-theme they judged most important and the lowest score of 1 to the issue they judged least important.

Sub-themes	Total score (max-128)	No. of individual issues	Median	Mean	Standard deviation
Relationships and understanding *e.g. storytelling about choice, clear understanding of what is involved, trustworthy information*	113	7	15	14.1	1.9
Protection/efficacy *e.g. expensive vaccines for free, protection for my child from illness*	100	5	12.5	12.5	2.6
Disease awareness *e.g. direct protection from serious illness, more likely to take part if I know someone who suffered from the disease*	96	2	13.5	12.0	4.0
Economic compensation *e.g. compensation for risk, costs of involvement including time, effect, expenses*	95	4	11.5	11.9	2.5
Benefits to society *e.g. contribution to public health, the value of the study for future generations*	90	8	11	11.3	3.8

Values/culture *e.g. conflict with values, future relationship if child disagrees with his participation at a later date*	85	3	10.5	10.6	3.7
Increased access to health care professionals	76	2	10.5	9.5	4.7
Media *e.g. good news about vaccine potential, put off by news articles*	75	2	9	9.4	3.4
Presumptions *e.g. a health child?*	70	1	8.5	8.8	1.6
Time/effort *e.g. too much time involved*	69	1	7.5	8.6	3.6
Patient/parent concerns *e.g. concerns around any pain caused to the child by injections*	53	2	6	6.6	28
Infrequent but significant risks *e.g. I can demonstrate the safety of the vaccine, anxiety for child's health during the trial*	42	4	5	53	3.5
Placebo *e.g. participants expect to be in treatment not placebo arm*	42	2	3.5	5.3	3.7
Side effects *e.g. after effects unknown, uncertainty over negative side effects*	40	5	5	5.0	2.1
Anti-vaccine lobbyists *e.g. high levels of refusals to vaccinate, bad news about vaccine effects*	26	2	2	3.3	4.4
Negative perception of vaccines *e.g. negative rumours on vaccines, vaccines are not 100% safe / effective, there are too many vaccines*	16	5	2	2.0	1.1

Relationships and understanding

Seven issues were grouped under the sub-theme of *'relationships and understanding'.* This sub-theme was perceived to be positive, and trustworthy and clear information was key so that any person considering taking part in a trial is aware of exactly what is involved from start to finish. This is essential, not only within the consent documents but also when in communication with researcher. One participant also highlighted the positive influence of the recommendation for participation in a trial coming from someone they trust and gave examples such as a doctor, patient group or midwife.

The Nuffield Council on Bioethics (2015, paragraph 5.8) identified trustworthiness, openness and courage as key professional virtues when conducting research with children. They suggest that children and their parents will only agree to take part in research if they can trust both the researchers and the way the research is structured. In addition, the Council highlights the need for researchers to be clear and honest in communication with research participants, throughout the entire study.

Two of the issues grouped within this sub-theme related to the need for a compelling story clearly setting out what is involved when participating in a vaccine trial *'good storytelling of doctor'* and *'storytelling about choice'.* This underlines the importance of this issue to these

participants who agreed that it was the most important sub-theme in the comprehension nominal group.

The relationship between researcher and patient was also a sub-theme in the comprehension nominal group. Although it did not rank as highly in importance as under the current theme, the consistency in issues and sub-themes raised by participants is re-assuring.

Protection/efficacy

Of the five issues grouped into the sub-theme of 'protection/efficacy' four focused on positive outcomes of participation in a clinical trial, such as the opportunity to benefit from a vaccine which may otherwise be expensive or currently unavailable to wider society. The final issue focused on the potential for uncertainty on the behalf of the patient around the benefits of participation for themselves or others. This may be viewed as a negative factor when considering whether to take part in a vaccine trial. Overall, however, the combined scores suggest that this sub-theme was viewed positively.

These points are reflected in a study by Newman et al (2004) which explored the concerns, motivations and intentions in HIV vaccine trials among adults. This study found that patients indicated several motivating factors for taking part in the trial including protection against the HIV infection, the endorsement of the vaccine by trusted authorities and to improve their overall health.

Similarly, a review of 46 studies by Tromp et al (2016) found that personal health benefit is one of the key motivating factors for parents and children considering whether to take part in a clinical trial. This however, also becomes problematic in situations where no direct benefit exists. The review found that children are particularly vulnerable to therapeutic misconception and where there is no prospect of a direct health benefit, children will frequently cite therapeutic benefits as a key motivating factor. This again suggests that clear and honest information from the researcher is essential.

Disease awareness

The two issues included within the sub-theme of *'disease awareness'* were focused on an increased likelihood to take part if the participant has direct experience of the disease or if a person is motivated to participate because they may receive direct protection from a serious illness. The latter issue overlaps with the *'protection/efficacy'* sub-theme and should probably have been grouped there.

Nevertheless, the fact that *'disease awareness'* was collectively ranked as the third highest priority for encouraging participation in clinical trials, demonstrates that personal experience

is key. Although personal experience occurs outside of the IC process, there may be other ways it could be incorporated such as through case study examples to demonstrate the impact of the disease.

The influence of direct experience on likelihood to participate in a clinical trial is demonstrated within research. A study by Trauth et al (2008) showed that having a relative or friend who has an illness as well as those with prior experience with participation in a medical research study are key determinants of whether someone would be willing to take part.

Economic compensation

The sub-theme of economic compensation included issues around compensation for the risk of participation as a motivating factor as well the time and effort of participation as a deterrent. Participants considered the financial and non-financial costs of involvement and whether they would be reimbursed for their expenses. In reality, as financial incentives for participation in clinical trials are considered ethically unacceptable, compensation is only paid for travel expenses or to compensate for the time spent as part of the study (Grady, 2015).

One participant specifically referenced time spent travelling and explained that an honest dialogue around the expectations of participants is highly important: *"… going two miles down the road is quite different to going to a major centre 25 miles away."* Again, this relates back to the need for clear and honest information about the trial from the beginning.

Benefits to society

Issues grouped into the sub-theme of *'benefits to society'* referenced the altruistic benefits of participation in a trial: *'contribution to public health', 'the greater good'* as well as the importance of clinical trials to the advancement of medicine: *'the value of the study - to future generations', 'thinking about future children'.* The group also identified a potential misconception patients may have around the outcomes of the clinical trial: *'After this trial, what will happen? – [will] all children will have this vaccine? (UK)'*. Participants collectively ranked this as the fifth most important factor when considering whether to take part in a vaccine trial, considerably lower than the above sub-themes, however the fact that this sub-theme generated eight individual issues indicates that participants were engaged with this topic.

Altruism had been previously been cited within the literature as a key motivation for participants. In fact, Detoc (2017) found that altruism was the most commonly cited motivation for participation in vaccine trials. However, these findings suggest that other factors such as the opportunity to be protected against a disease and a clear and honest communication from

the research team may be more persuasive for individual deciding whether to participate in a vaccine trial.

6.2.2. Factors discouraging participation in a vaccine trial

The combined ranking scores for the question of what might put someone off taking part in a vaccine trial are shown in Table 5. In this instance, *'Negative perceptions of vaccines'* is the most important sub-theme with a total score of 122 out of a maximum of 128, and an average score of 15.3 (SD = 1.2). There was strong consensus amongst the group on the importance of this sub-theme. *'Anti-vaccine lobbyists'* were scored as the second most important discouraging sub-theme, with a total score of 106 and an average score of 13.3 (SD = 2.2). These two sub-themes were ranked respectively as least and second least important encouraging factors. These were the only two sub-themes in which ranking as positive factors was precisely the reverse of their ranking as negative factors. These were also the sub-themes with the clearest bias in wording (*'negative' perception, 'anti'-vaccine*) in contrast to the other themes which were more neutrally worded. For example *'protection/efficacy'* would be expected to be a positive influence where there is evidence of efficacy but much less so if evidence is lacking, while *'side effects'* would be a more powerfully negative influence if significant side effects were known and predicted than if side effects were considered mild or unlikely.

'Infrequent but significant risks' were rated as the third most important factor with a collective score of 104 and an average of 13 (SD = 2.5).

Table 5: Patient expectations: sub-themes are shown in the order prioritised by participants when considering what might put them off taking part in a vaccine trial. Participants awarded the highest possible score of 16 to the sub-theme they judged most important and the lowest score of 1 to the issue they judged least important.

Sub-themes	Total score (max-128)	No. of individual issues	Median	Mean	Standard deviation
Negative perception of vaccines	122	5	16	15.3	1.2
Anti-vaccine lobbyists	106	2	14	13.3	2.2
Infrequent but significant risks	104	4	12.5	13.0	2.5
Values/culture	94	3	11.5	11.8	1.8
Media	81	2	9.5	10.1	4.1
Patient/parent concerns	80	2	10.5	10.0	3.2
Side effects	73	5	9	9.1	4.1
Time/effort	68	1	11.5	8.6	4.9
Placebo	59	2	7	7.4	5.3
Presumptions	54	1	6.5	6.8	2.8
Relationships and understanding	53	7	6.5	6.6	4.1
Disease awareness	45	2	4.5	5.6	4.4
Protection/efficacy	43	5	5.5	5.4	2.5

Economic compensation	42	4	5	5.3	2.4
Benefits to society	34	8	4.5	4.3	3.1
Increased access to Health care professionals	30	2	3	3.8	2.0

Negative perception of vaccines

During the clarification stage, five issues were grouped under the sub-theme of *'negative perception of vaccines'*. All the issues generated focused on negative views of vaccines which are evident within the wider-population, but which participants conceived as vaccine myths, such as *'vaccines are not effective', 'vaccines are not good for the immune system'* and *'there are already too many vaccines'.*

Although negative perception of vaccines is a key influence against taking part in a vaccine trial, it is not necessarily likely to be part of the consent process in terms of either the interaction between the researcher and patient or the IC document. The issues underlying negative perception of vaccines are societal factors, likely to be beyond the influence of the consent process.

Anti-vaccine lobbyists

'Anti-vaccine lobbyists' ranked as the second highest priority deterrent to taking part in a vaccine trial and is invariably intertwined with *'Negative perceptions of vaccines'.* The two issues grouped into this sub-theme focus on negative news stories on vaccine effects and how a high level of refusal to vaccinate might impact wider society. One participant provided an example of how an anti-vaccine stance can have an effect on wider society: *"In Ireland, for example, the cervical cancer vaccine has been heavily attacked by religious groups… This has had a high impact on whether people have or have not accepted the vaccine."* There is a large body of literature (Dubé et al, 2014) which documents the negative impact of anti-vaccination movements on vaccine uptake rates. The influence of anti-vaccine movements varies over time and between countries, and all participants' countries have either currently or in the past suffered from anti-vaccine activity with resulting outbreaks of preventable diseases. Fears about the safety of vaccines propagated by such groups have a negative influence on recruitment to vaccine trials as well as the uptake of routinely offered vaccines in national programmes (Detoc, 2017).

Infrequent but significant risks

Four individual issues were grouped under the sub-theme of *'infrequent but significant risks'.* They included issues from both a positive: *'I can demonstrate the safety of the vaccine tested'*

and negative perspective: *'Potential anxiety for [my] child's health for many years'*. However, when asked during the ranking stage what might put them off participating in a vaccine trial the group perceived this sub-theme negatively leading to a high combined score. Conversely, *'infrequent but significant risks'* scored as the fifth least important factor in encouraging participation, again, indicating this sub-theme was viewed negatively overall.

This supports Kulkarni's (2013) view that there is a low tolerability of adverse effects within vaccine trials. This is because the target population for vaccine trials are healthy people, and frequently children and infants. This factor also links back to the need for a more balanced view of the risks and benefits so that the risks do not appear to be out of proportion in comparison to any perceived benefits of participation.

Values and culture

This sub-theme is expressed in entirely neutral terms, and appears in the middle of both tables. However, in the ranking it was more powerful as a negative factor (ranking fourth) and was only the sixth most important factor for encouraging participation. This may be because all three individual issues grouped within this sub-theme are negative influencers. They include the potential for disagreement between a couple regarding participation in a vaccine trial and concerns around whether a child who has participated in a vaccine trial could disagree with their involvement once they reach adulthood. The final issue relates to the possibility that participation in a vaccine trial could conflict with the participants cultural values.

The group discussed the impact of cultural factors and considered whether an individual might be less likely to participate if the vaccine would not be relevant to them: *'if there was a vaccine that could protect you against cirrhosis of the liver but you think, "I never drink" so why would you get this vaccine?'*

The wider role of culture in relation to participation in vaccine trials, for example the influence of social and cultural differences on understanding, or the need to provide support during the IC process for families from different cultural backgrounds was not discussed in any detail during the workshop.

6.3. Theme 3: Assent

What are the challenges of recruiting children to take part in a vaccine trial? Consider how the consent/assent process involves the child, parent and researcher.

In the round robin stage the nine workshop participants collectively generated 51 ideas which were grouped into eight clarified issues shown in table 6. The greatest number of individual

post it notes was generated under the sub-theme of communication, however as this group contained a diversity of issues, for the purposes of analysis it has been broken down into three topics.

Despite the question asking the group to focus on the challenges of recruiting children to take part in a vaccine trial, respondents frequently cited solutions alongside current issues. Testing understanding received the highest score, achieving 60 points out of a possible 72. On average, participants scored this 6.7 points (SD = 1.9). Testing understanding was closely followed by family dynamics which received a total of 57 points and on average a score of 6.3 points (SD = 1.2). Communication was rated the next most important issue with an overall score of 53, and on average an individual score of 5.9 points (SD = 1.6).

Table 6: Assent: sub-themes shown in order prioritised by participants. Participants awarded the highest possible score of 8 to the sub-theme they judged most important and the lowest score of 1 to the issue they judged least important.

Sub-themes	Total score (max-72)	No. of individual issues	Median	Mean	Standard deviation
Testing understanding *e.g. ensuring those involved fully understand requirements of trial through testing or through asking researchers questions*	60	12	7	6.7	1.9
Family dynamics *e.g. who is involved in the decision to consent? The difficulties of dealing with disagreements within family*	57	11	6	6.3	1.2
Communication	53	18	6	5.9	1.6
Impact on daily life *e.g. physical after effects and concerns surrounding change to habits*	38	2	4	4.2	1.6
Emotional response *e.g. worry whether you are making the right decision for child*	36	2	4	4	2.2
Friendships *e.g. children being concerned what their friends think – could be encouraging or discouraging*	36	3	4	4	2.1
Society *e.g. benefit for the health world*	24	2	2	2.7	2.4
Change in circumstances *e.g. what if a child/teen decided to interrupt the trial process?*	20	1	2	2.2	1.0

Testing understanding

There was a cohesive collection of issues under this sub-theme on testing understanding: *'Some way of validating child's and parents understanding of trial/requirements', 'Researcher - Can I be sure that the child understands what will happen?', 'Ensuring parents/carers and child all fully cognisant of what's involved'.* Participants discussed having *'independent assessors to verify that people understand'* and the importance of parents understanding what the benefits vs the risks are to the child.

It might have been expected that testing understanding would have been discussed in detail under the theme of comprehension, however it only fully emerged under the assent theme. From this we can infer that participants felt a greater need to verify the understanding of children as potential participants in vaccine trials, perhaps perceiving a greater obligation to protect children due to their vulnerability.

Some issues included within this sub-theme focussed on the more loosely related idea of both parents and children having the opportunity to talk to researchers individually, *'space for child to ask questions, maybe with/without parents present if sensitive in nature'* and *'parent's [should be able to] ask Q's [questions] without child being present'.* There was extensive discussion amongst participants of the need for individual, private conversations with the researcher particularly in relation to trials of vaccines against sexually transmitted infections such as HPV, given that parental permission may be associated with risks such as inadvertent disclosure of an adolescent's sexual orientation or risk behaviours, an imperative discussed in the literature (Alexander et al, 2015).

Family dynamics

Family dynamics was ranked as the second most important issue, scoring 57 out of a possible 72. On average, participants scored this issue 6.3 (SD = 1.22). Under family dynamics the group were predominantly concerned with how decisions about participation were taken, with the best case scenario being a group decision between the child, parent and researcher, and problems arising when there is disagreement between parents and children. The group discussed disagreements within a family as being a barrier in the assent process, both when a child wants to take part, but their parent/carer does not agree, and in where the child experiences parental pressure to take part.

Issues generated under this theme suggested that the way in which the consent/assent process worked would be different in different families: *'strong parents = strong child', 'the child is fragile - depend on their parents', 'children - depends on his personality/age: might do it to please/to reject his parents'.* In the ensuing discussion, participants agreed that in some families the child is used to obeying parents and would expect the parents to decide, while in other

families the child would expect to have more autonomy. This supports existing literature which suggests that the extent to which a child engages with the decision making process is dependent on pre-existing relationships (Pinxten et al, 2008). One participant commented that, *'it [information on the trial] might well not get to the child if the parents didn't want to take part in the first place.'*

It was acknowledged that in addition to practicalities, such as the availability of a parent/carer: *'Parents - time needed/balance other family commitments'*, decision-making within relationships may be influenced by social and cultural context. For example, one participant suggested that *'…there might be some cases where it's not a mutual decision between parents, it's actually the father that gets more of a say or is more involved than the mother. Or in single parent households you've only got one parent who needs to make the decision.'*

In addition to the influence of family dynamics and socio-cultural considerations, the law determines whether only one or both parents are required to consent for a child to participate in research. For example in Italy and the Netherlands both parents are required to consent, whilst in Spain, Republic of Ireland and United Kingdom, only one parent is (EMA, 2016). As representatives from these five countries attended the workshop, their views are likely to have been heavily influenced by the laws in place in their country of residence.

Interestingly, in our workshop, friendships were perceived to have a relatively low influence in the assent process, yet Alexander et al (2015) revealed that when adolescents were asked to consider participating in a HIV vaccine trial, peers were identified as the individuals they would most frequently talk to, followed by health care workers, family and other adults. As previously discussed, adolescents enrolling in trials for vaccines against sexually transmitted infections may be less likely to consult family, hence more inclined to seek guidance from peers due to the sensitive nature of the trial.

The current model of assent does not acknowledge the pre-existing hierarchies that exist within most families, and the social content in which decisions are made (Alderson et al, 2006; Snethen et al, 2006; Miller et al, 2008). Indeed, adolescents are considered in society, to be in a socially less powerful position compared to the adults (Alexander et al 2015), yet the current informed assent process seemingly disregards this, and assumes that children and parents will have an equal role in the decision making process. This can create difficulties for researchers attempting to enrol children and teenagers in trials, particularly where there is disagreement or perceived disagreement between parent and child on whether to take part.

Communication in informed assent

After family dynamics, the group considered problems with communication to be the next major challenge in recruiting children to vaccine trials. Within this sub-theme a diversity of issues were discussed, therefore for the purposes of analysis we have further divided this sub-theme into three topics.

- Clear and honest communication from the researcher

There were suggestions that the researcher should have a good relationship with the child and parent, with the ideal scenario being the researcher, child and parents working as a team. The group also stressed the importance of the researcher being honest about the opportunities and risks, and providing realistic timescales for the trial. During this discussion, being able to trust the researcher was emphasised, with one participant describing the opinion of a patient's personal, family Doctor as particularly valuable. This is congruent with the sub-theme of relationships between participant and researcher which emerged in the two previous nominal groups.

- Tailored communication for the child

There was a discussion around tailoring the information to respect the age and ability of the child. This includes the researcher using appropriate language and considering the level and type of information suitable for children. For example, one participant suggested that there may be some information that might not be appropriate for children *'So what do children need to know? Are there things that are not appropriate for all audiences? Maybe that's a challenge because there might be things that parents don't want their child to know.'* Another participant described *'moving in the world of the child, and being at the same level as the child*' as a way of ensuring appropriate and effective communication.

- Digital communications/social media

The potential benefits of using digital tools was briefly discussed under the comprehension theme, in that it offers a way to develop informed consent documents that are accessible for all, however assent was the only theme in which the topic of social media emerged. Therefore, there appears to be a specific association with social media and younger audiences, with participants making comments such as *'Use the social media and communication, especially for children' 'It's just that the older generation are used to paper and they [children/adolescents] use apps and You Tube.'*

Similarly to the comprehension theme, the importance of a child understanding why they are being asked to take part and why the trial is important, in a way that makes sense to them, emerged as an important issue under communication. However unlike in the comprehension theme where this issue was deemed the most important, under the assent perspective, it was considered to be a priority only after testing understanding and the influence of family dynamics.

Change in circumstances

In table 6, the sub-theme ranked as the least important was *'change in circumstances',* which contained just one issue *'researcher – what if the child/teen decides to interrupt the process.'* However, during the workshop, the group had a detailed discussion about how the behaviour of teenagers could influence their recruitment and retention to a trial. For example, comments included *'if he is a teenager… for example he might decide to join [a trial] to rebel against his parents. To do the opposite', 'They are at an age where they will easily change their minds and you don't know why.'*

Whilst the group were in agreement that this was a valuable suggestion, they had difficulty in agreeing on an appropriate title for this sub-theme. For example, an initial suggestion of *'age related issues'* was rejected on the basis that children and teenagers could change their minds about participation, but their reasoning is likely to be different, i.e. younger children might prioritise being selected for a school play, whilst adolescents might choose to prioritise new relationships. As a result it was decided that *'change in circumstances'* encompassed this discussion, however it is somewhat ambiguous, and perhaps contributed to it being perceived as having little importance.

6.4. Theme 4: Gender

What might different genders consider when providing informed consent?

The final nominal group focused on the theme of gender and generated 30 individual issues which were grouped into eight sub-themes.

As shown in Table 7, the sub-theme of *'communication'* received the highest score of 59 points out of a maximum of 72. The average score was 6.6 (SD = 1.2). The sub-theme of *'relationships'* received the second highest score of 55 and an average of 6.1 (SD = 1.9). As well as receiving the highest ranking scores, these two sub-themes contained a greater number of issues. This adds weight to the consensus within the group that communication and relationships were the most important factors within the theme of gender and informed consent.

The final six sub-themes will not be discussed in detail in this report, due to the drop off in scores at this point. However, it is worth noting that whilst all other participants scored 'contraception/trial' as the least or second least important priority, one participant gave it the highest possible score of 8.

The standard deviation of mean scores for the sub-themes discussed within this theme is relatively low (between 1 and 2.4), indicating considerable strength of consensus on the priority of sub-themes.

However, there were several indications that participants were less engaged with the gender theme than the other themes discussed:

- Fewer ideas were generated during the round robin stage: 30 compared to more than 50 ideas each for the themes of assent, comprehension and patient expectations. This may have also been an effect of participant fatigue, as the the gender theme was discussed at the end of the workshop, which ran for eight hours over a one day period.
- During the round-robin and discussion stages, participants continually referred to the specific circumstances set out in the scene-setter used to introduce the gender theme. Scene-setters were used in all four nominal groups to aid discussion and stimulate ideas, but it was only during the gender theme that the scenarios portrayed in the scene-setter tended to dominate discussion. This may have been partly due to the use of story boards as the scene setter, which were used because a suitable video, as was shown for patient expectations and children's assent, could not be located (although story boards were used in the pre-read to introduce the patient expectations and assent themes).
- Finally, at the end of the workshop participants were asked to complete an Evaluation Form to collate feedback on the session. When asked which of the four themes they found most interesting or useful, none of the participants identified gender and all identified one of the other three themes.

Participants thus appeared to have difficulty engaging with the gender theme, or found it less important to the topic of informed consent than the other themes.

Table 7: Gender: sub-themes shown in order prioritised by participants. Participants awarded the highest possible score of 8 to the sub-theme they judged most important and the lowest score of 1 to the issue they judged least important.

Sub-themes	Total score (max-72)	No. of individual issues	Median	Mean	Standard deviation
Communication *e.g. speaking to a researcher of the same sex, potential that men and women may have different questions about the trial, opportunities for individuals in a school setting to ask questions privately*	59	9	6	6.6	1.2
Relationships *e.g. should the partner of a pregnant woman entering a trial give consent? Should one or both parents give consent for their child to enter a trial?*	55	7	7	6.1	1.9
Decision making for children *e.g. not wanting to cause pain for child, decision making for single parents*	47	3	5	5.2	1.3
Risks to mother/child *e.g. risks to pregnant woman and baby, men may be more risk averse for vaccines for their child if uncertain of risks/benefits*	45	4	6	5.0	2.0
Decision making in pregnancy *e.g. consent needed from father of baby?*	40	2	4	4.4	2.4
Practicalities *e.g. which parent will take the child to appointments/deal with any side effects? Key differences between men and women*	38	3	5	4.2	2.1
Assumption based on gender *e.g. role versus gender*	21	1	2	2.3	1.0
Contraception/trial *e.g. should this only be the responsibility of the woman?*	19	1	1	2.1	2.3

Communication

Nine issues were identified as relating to the sub-theme of *'communication'.*

Two issues referenced the impact of gender-based communication differences. Participants suggested these differences may affect the patient/researcher relationship and noted the potential benefits of a patient having access to a researcher of the same sex. This was in reference to the scenario described in the scene-setter in which a teenage girl is being recruited to an HPV vaccine trial, which is a sensitive situation.

This is supported in the literature and is comprehensively described in deliverable 1.2 within Work Package 1 of the I-Consent project, in the report entitled *'Report on gender and age-related issues associated with the acquisition of informed consent'*. Existing gender-based assumptions impact the patient/physician dynamic within a clinical setting, influencing both the way health professionals communicate with patients and the way patients treat health professionals. Bertakis et al (1995) suggest that female physicians engage in more positive conversations, they ask more questions and provide more information. Deliverable (1.2) for Work Package 1 explains that female doctors are identified by patients as being more positive and tend to be rated as more satisfactory. This view is heightened if the patient is female. At this stage, it is worth referencing one issue around *'making gender-based assumptions'* and attributing characteristics to men and women. This issue was grouped as a sub-theme in itself and ranked as the second lowest priority but is worth discussing under *'communication'* as the two are invariably connected. The discussion focused on the dangers of making generalisations in relation to the behaviours of men and women, *'I would question whether that [risk aversion] is even anything to do with gender and whether we should even go down that road to attribute certain characteristics to certain genders.'*

Another participant then went on to suggest that some assumptions regarding the roles adopted by men and women are grounded in truth. Referencing the scene setter, one participant explains: *'It's quite likely that Holly will have told her mum that [she's on the contraceptive pill], but she probably won't have told her dad. That's just the way the world works and it's unlikely to have been the other way round… There may be things which are shared more with the female parent, assuming that it's a couple that's a male and female, so in terms of impacting the decision making it may be that mum has more information about the child.'*

A study by Alexander et al (2015) supports the view that the mother is more likely than any other family member to be consulted on medical issues, and this is particularly evident amongst female trial participants. The most frequently cited reasons for consulting the mother include valuing her opinion, her knowledge of the medical field and because she is likely to drive them to appointments.

Participants also put forward a number of additional issues relating to communication in the scenario of a teenager considering participation in an HPV trial. They highlighted the importance of providing time and space for the teenager to speak to a researcher and ask questions in private. They also referenced the discrepancy between the age of consent for clinical trials and for receiving medical treatment such as the contraceptive pill. The other issues were specific to the scenario described in the scene setter and will not be discussed further in this report.

Relationships

'Relationships' scored as the second highest priority. This sub-theme included a range of issues and so for the purpose of analysis they have been grouped into three topics; pregnancy, parental consent and the cultural / social dynamic.

- Pregnancy

Participants discussed the controversial topic of consent during pregnancy and questioned whether it is appropriate for the partner of a pregnant woman to give consent for her to participant in a clinical trial. One participant felt that the views of both parents should be considered when the pregnant woman or unborn child is at risk, however minimal that risk may be: '*In pregnancy it is important to have consensus from the partner. The partner may feel quite strongly that they should agree to this as well.*

Other participants felt strongly that the pregnant woman's autonomy must be prioritised. One participant in particular expressed a concern that the need to formally include the partner within the consent process could jeopardise the rights of the mother: *'Can I just flag up that I'm uncomfortable that there's an element of taking control away from the woman about her body... Women have come a long way in terms of having control over their bodies when they're pregnant… It's the decision making that I'm uncomfortable about.'*

This view is backed up within the principles described by the American College of Obstetricians and Gynaecologists Committee on Ethics, which explain that consent from the partner of the pregnant woman is not necessary or ethically justified except in a few specific cases. Consent from the partner is required when there is more than a minimal risk to their exposure to an investigational agent, if personal data will be collected on the partner or if the testing of a partner is required for a woman to participate in a study (ACOG Committee on Ethics, 2015).

Similarly, the Belgian Advisory Committee on Bioethics (2004) has discussed the status of the partner when a pregnant woman is enrolled in a clinical trial. Whilst some members of the committee agreed that the autonomy of the pregnant woman must be prioritised, other members suggested that as pregnancy involves two parents, the responsibility of the father must be considered. In case of conflicts, participation in a clinical trial should therefore be denied.

- Parental consent

An issue identified by one participant referred to a mother giving consent for her child to participate in a trial despite her husband's disagreement. The group raised the issue of the

legality around this scenario and agreed that in a stable relationship the partner should ideally be involved in the decision making process.

As workshop participants were based in five different countries, this must be recognised within the context of the debate as the number of signatories legally required for a child to participate in a clinical trial varies between countries. In the Republic of Ireland, Spain and the UK only one signature is required whereas in Italy and the Netherlands, a signature is required from both parents.

Another issue referenced the dynamics between a child and their parents and the group considered whether a child is more likely to confide in one parent over another. A very similar issue was grouped and discussed within the sub-theme of *'communication'* / *'gender-based communication differences'*. Several participants again suggested it was more likely that a female child would confide in her mother rather than her father, although this was not unanimous.

- Cultural / social dynamic

Two ideas within this sub-theme related to the social or cultural standing of individuals within a relationship and the impact this may have on consent for a trial: *'Maternal/child vaccine - family/cultural dynamics may play a part in decision making'* and *'Man - my wife does have a lower cultural background compared to mine. I fear she doesn't understand what she signed'*. The latter idea generated amusement and conversation about sexism in relationships, but also acknowledged the fact that in some contexts women are not permitted to take decisions for themselves.

Women who are not permitted to give consent for themselves and require permission from a spouse or male relative to participate in research due to cultural factors should be considered socially vulnerable in research. The CIOMS guidelines explain that researchers need to exercise special care when recruiting women in these situations for clinical trials (CIOMS 2016, Commentary on Guideline 15, V4). They need to pay particular attention to *'the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them'* (CIOMS 2016, Commentary on Guideline 18, V4).

7. Conclusion

The participants felt strongly that IC documents should connect with patients, presenting a clear case for participation and offering a compelling story. They agreed, as a group, that the example IC document failed to explain to the patient why they should take part in a trial in a way that is relevant and meaningful to them. This demonstrates a fundamental flaw with IC documents and represents a significant barrier to participation.

The group agreed that risks and benefits should be presented in a balanced way. They highlighted an imbalance in the way that potential risks and benefits of participation were described within the example IC document. The inclusion of excessive risk information was attributed to the sponsor, in that this information was perceived to be included, not to ensure that patients were well informed, but rather to reduce the liability of the sponsor in case of an adverse event occurring. One suggestion for enabling a more balanced view of the risks might be to include comparisons with the level of risk involved in situations which are more familiar to patients, such as the likelihood of having a car accident or winning the lottery.

Participants explained that one of the top motivating factors for taking part in a vaccine trial may be to gain protection from a disease, either for themselves or for their children. This echoes the consensus that the IC document should clearly show the case for why, presenting a compelling story, including information to enable potential participants to understand the disease that a vaccine might offer protection against.

For the participants, trustworthy and clear information is key. This point is relevant not only within the consent document but also in communication between researcher and patient. The importance of communication, trust, and the relationship between researcher and patient emerged in nearly all of the nominal groups.

Conversely, a lack of trust was viewed as a key demotivating factor. A particular instance of this was the idea raised by some participants that the IC document was written in line with the sponsor's interests as opposed to those of the patient. A practical suggestion was that sponsor information should not appear at the beginning of the document. Participants agreed that it was helpful to include a statement about ethical approval at the beginning of the document to show that it had been scrutinised by independent authorities and could therefore be trusted.

The group provided other practical suggestions about improving the structure of the IC document, such as including a lay summary at the beginning, and/or a flowchart explaining the what's involved in the trial and summarising the sections/lay out of the IC document, and the importance of using simple language and avoiding medical jargon.

With reference to the theme of assent, a situation in which the child, parent and researcher work closely as a team was agreed upon by participants as being the ideal scenario within the consent process. This, however, may be difficult to implement in reality, as the extent to which a child is involved in the decision making process depends on pre-existing factors such as their personality, and their role within the family hierarchy.

Tailoring communications for the participant was of particular importance in relation to children's assent. Participants agreed that information must be sensitive to both the age and ability of the child, and use appropriate language. Linked to this, the group agreed on the benefit of introducing comprehension tests for children to ensure a level of understanding on behalf of the child. Digital communications were referenced as an appropriate means of communication with younger people but interestingly, the topic did not appear as a possible solution within the discussion around comprehension, as has been discussed extensively within literature (Cummings and Rowbotham, 2017; Stevens et al 2016).

The group felt strongly that a pregnant woman's autonomy must not be compromised in the process of informed consent for research. Although this issue was discussed in relation to concerns around formally including the partner within the consent process, it also relates to the topic of communication. There are some situations in which researchers need to be aware of gender issues, depending on the sensitivity of the topic. In certain circumstances, for example trials of vaccines against sexually transmitted diseases, or involving pregnancy, many patients may prefer to be seen by a doctor of their own gender. There is also some evidence that female doctors are perceived as being more likely to engage in positive conversations and tend to be rated as more satisfactory by patients (Bertakis et al, 1995; I-Consent Work Package 1 deliverable 1.2, 2018).

Despite suggestions that gender influences the doctor / patient dynamic, the group were uncomfortable about the risk of gender stereotypes being used as the basis for communication within the IC process. Participants felt that although gender-based communication differences exist, they are not categorical and it should not be assumed they apply to all females or all males. In general, this seems to align with Poyatos (2002), who notes that although gender is a conditioning factor of communication activities, it is not the only or the most important. Therefore, the group consensus was against tailoring the IC process towards gender and felt it should instead be better tailored to the characteristics and needs of the patient.

8. Limitations of the study

- As not all of the workshop participants' had personal experience of the full IC process (including coversations with the researcher) their understanding was mostly limited to the IC document which was circulated as part of the pre-read exercise. Had the participants all had the same depth and breadth of knowledge about IC, the issues they raised and priortised may have been different.
- There was a gender imbalance amongst the workshop participants, with seven females and just two males. This is of particuar significance as gender was discussed as a topic in itself and may have led to a gender-bias in the issues raised.
- As no minors or adolescents were included in the workshop, the participants are unlikely to fully represent the perspectives of teenagers/minors. This may explain why, within the context of the assent theme, friendships were considered to have little influence compared to the importance of family dynamics.
- Within the discussion around the theme of gender, participants frequently referenced the storyboard examples which were shown during the theme introduction. Participants may have found gender to be a particularly difficult theme, hence their reliance on the scene setter. Participants were wary of falling back on gender stereotypes in their discussion and the resulting self-censorship may also have limited discussion.
- During the patient expectations section a decision was made to change the ranking method. This decision was made live during the workshop. It is possible the last minute change of method was particularly difficult for some participants, who may not have contributed equally to the resulting prioritisation of sub-themes.
- After the first nominal group was completed, time restrictions meant that the combined ranking scores were not presented immediately after each nominal group, as was initially anticipated. Instead, the combined scores for sub-themes within the patient expectations, assent and gender themes were presented back to the group at the end of the workshop. For this reason the participants were not given the opportunity immediately after each discussion to change the priority order of the sub-themes.
- The workshop ran for eight hours and although there were regular breaks, participants were fatigued by the latter part of the day. We reported less engagement with the gender theme and this might have been exacerbated due to it being the final theme of the day.

9. Acknowledgements

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Group B Strep Support

Meningitis Now

Nederlandse Meningitis Stichting

The Dutch Liver Patient Association

10. References

ACOG Committee on Ethics (2015) Committee opinion, *The American College of Obstetricians and Gynaecologists Committee on Ethics.* Number 646. Available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Ethics/co646.pdf?dmc=1&ts=20180423T1030545071

Alderson, P., Sutcliffe, K. and Curtis, K. (2006) Children as partners with adults in their medical care. *Archives of Disease in Childhood*, 91(4):300-303.

Alexander, A.B., Ott, M.A., Lally, M.A., Sniecinski, K., Baker, A. and Zimet, G.D. (2015) Adolescent decision making about participation in a hypothetical HIV vaccine trial. *Vaccine*, 33(11):1331-7.

Belgian Advisory Committee on Bioethics (2004) Opinion No. 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women. Available at: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/opinion_31_expos_femme_enc_et_all.pdf

Bertakis, K.D., Helms, L.J., Callahan, E.J., Azari, R. and Robbins, J.A. (1995) The influence of gender on physician practice style. *Medical Care*, 33(4):407-16.

Cameron, D. Gender. In: Brown, K. editor. (2006) *Encyclopedia of Language & Linguistics* (Second Edition). Oxford: Elsevier:733-9.

Council for International Organizations of Medical Sciences (CIOMS) (V1, 1982; V4, 2016), *International Ethical Guidelines for Health-related Research Involving Humans.* Available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

Council of Europe (1997) *Convention on Human Rights and Biomedicine*, available at: https://rm.coe.int/168007cf98

Grady, C., Cummings, S. R., Rowbotham, M. C., McConnell, M. V., Ashley, E. A. and Kang, G. (2017) Informed Consent. *The New England Journal of Medicine*, 376:856-867.

DasMahapatra, P., Raja, P., Gilbert, J. and Wicks, P. (2017) Clinical trials from the patient perspective: survey in an online patient community. *BMC Health Services Research,* 17(1):166.

Detoc, M. (2017) Barriers and motivations to volunteers' participation in preventive vaccine trials: a systematic review. *Expert Review of Vaccines*, 16(5):467-477.

Diamond, M. (2002) Sex and gender are different: sexual identity and gender identity are different. *Clinical Child Psychology and Psychiatry,* 7(3):320-334.

Dubé, E., Vivion, M. and MacDonald, N. (2014) Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. *Expert Review of Vaccines*, 14(1):99-117.

European Commission (2016) *Guidance on Gender Equality in Horizon 2020* (version 2). Available at: http://eige.europa.eu/sites/default/files/h2020-hi-guide-gender_en.pdf

European Commission (2017) Summaries of Clinical Trial Results for Laypersons, Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, 1-30. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf

European Medicines Agency (2016) Annual Report 2016, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2017/05/WC500227334.pdf

European Parliament (2001) The *clinical trials directive 2001/20/EC*, available at: https://ec.europa.eu/health/human-use/clinical-trials/directive_en

Frisaldi, E., Shaibani, A. and Benedetti, F. (2017) Why we should Assess Patients' Expectations in Clinical Trials. *Pain and Therapy*, 6(1):107–110.

Grady, C. (2015) Enduring and emerging challenges of informed consent. *The New England Journal of Medicine*, 372:855-62.

Grady, G., Touloumi, G., Walker, S.A., Smolskis, M., Sharma, S., Babiker, A.G., Pantazis, N., Tavel, J., Florence, E., Sanchez, A., Hudson, F., Papadopoulos, A., Emanuel, E., Clewett, M., Munroe, D. and Denning, E. (2017) A randomized trial comparing concise and standard consent forms in the START trial. *PLoS One,* 12(4).

Hidalgo-Tenorio, E. Genderlect. In: Naples N, Hoogland R, Wickramasinghe M, Wong A, editors. The Wiley-Blackwell Encyclopedia of Gender and Sexuality Studies. USA: Wiley 82 Blackwell; 2016. 1–4 p.

ICH (1996) *Guideline for good clinical practice E6 (R2)*, available at: http://ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Knepp, M.M. (2014) Personality, sex of participant, and face-to-face interaction affect reading of informed consent forms. *Psychological Reports*, 114(1):297-313.

Kulkarni, Prasad. (2013) Current topics in research ethics in vaccine studies. *Perspectives in Clinical Research*, 4(1):80-83.

Leibson, T. and Koren, G. (2015) Informed consent in pediatric research. *Paediatric Drugs*, 17(1):5-11.

Lorell, B.H, Mikita, J.S., Anderson, A. Hallinan, Z.P. and Forrest, A. (2015) Informed consent in clinical research: Consensus recommendations for reform identified by an expert interview panel. *Clinical Trials*, 12(6):692-5

McMillian, S.S., King, M. and Tully, M.P. (2016) How to use the nominal group and delphi techniques. *International Journal of Clinical Pharmacy*, 38(3):655–662.

Miller, V. A., Reynolds, W.W. and Nelson, R.M. (2008) Parent–child roles in decision making about medical research. *Ethics and Behavior*, 18:161–181.

Newman, P.A., Duan, N., Rudy, E.T., Roberts, K.J. and Swendeman, D. (2004) Posttrial HIV vaccine adoption: concerns, motivators, and intentions among persons at risk for HIV. *Journal of Acquired Immune Deficiency Syndromes*, 37(3):1393-1403.

Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, Nuffield Council on Bioethics, UK.

Nusbaum, l., Douglas, B., Damus, K., Paasche-Orlow, M. and Estrella-Luna, N. (2017) Communicating risks and benefits in informed consent for research: a qualitative study, *Global Qualitative Nursing Research,* 20(4)

Nystrand, M. (1986). *The structure of written communication: Studies in reciprocity between writers and readers*. Orlando: Academic.

Okoli, C. and Pawlowski, S.D. (2004) The delphi method as a research tool: an example, design considerations and applications*, Information and Management*, 42(1):15-29.

Pandiya, A. (2010) Readability and comprehensibility of informed consent forms for clinical trials, *Perspectives in Clinical Research,* 1(3):98-100.

Pandya, M. and Desai, C. (2013) Compensation in clinical research: the debate continues*, Perspectives in Clinical Research*, 4(1):70–74.

Pinxten, W., Nys, H. and Dierickx, K. (2008) Regulating trust in pediatric clinical trials. *Medicine, Health Care and Philosophy,* 11(4),439-444.

Poyatos, F. (2002) *Nonverbal Communication Across Disciplines: Paralanguage, kinesics, silence, personal and environmental interaction*. John Benjamins Publishing Company, Amsterdam/Philadelphia.

Sheehy, S. and Meyer, J. (2012) Should participation in vaccine clinical trials be mandated? *AMA Journal of Ethics*, 14(1):35-38.

Snethen, J.A., Broome, M.E., Knafl, K., Deatrick, J.A. and Angst, D.B. (2006) Family patterns of decision-making in pediatric clinical trials. *Research in Nursing and Health*, 29(3):223-232.

Stevens, N., Edwards, L., Balayah, Z., Hooper, R. and Knowles, C. (2016) Risk based survey evidence supports electronic informed consent as a recruitment method for UK clinical trials. *Journal of Clinical Epidemiology*, 77:134-141.

Stewart, D. and Shamdasani, P. (2015) *Focus Groups: Theory and Practice*, SAGE Publications, USA.

Stunkel, L., Bensin, M., McLellan, L., Sinaii, N., Bedarida, G., Emanuel, E. and Grady, C. (2010) Comprehension and informed consent: assessing the effect of a short consent form. *IRB,* 32(4):1-9.

Sully, B., Julious, S.A. and Nicholl, J. (2013) A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies, *Trials*, 14(166):8-9.

Trauth, J.M., Musa, D., Siminoff, L., Jewell, I.K. and Ricci, E. (2008) Public attitudes regarding willingness to participate in medical research studies. *Journal of Health and Social Policy*, 12(2):23-43

Tromp, K. (2016) Motivations of children and their parents to participate in drug research: a systematic review. *European Journal of Pediatrics.* 175(5):599-612

US Food and Drug Administration (FDA) (2014) Informed consent information sheet. Available from: https://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm

Van De Ven, A.H. and Delbecq, A.L. (1974) The effectiveness of nominal, delphi, and interacting group decision making processes. *The Academy of Management Journal*, 17(4):605-621.

World Health Organisation (2014) *European Vaccine Action Plan 2015-2020*: available at: http://www.euro.who.int/en/health-topics/disease-prevention/vaccines-and-immunization/publications/2014/european-vaccine-action-plan-20152020-2014

World Medical Association (1964) *Declaration of Helsinki*, available at: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

11. Annexes

Annex 1: Workshop invitation email template

Dear [INSERT NAME],

Informed consent in vaccine trials: your perspective

We would like to invite a representative of **[INSERT NAME OF PATIENT GROUP]** to take part in a **one day workshop** which **aims to identify ways to improve participation in vaccine trials**, with particular focus on human papillomavirus (HPV), meningitis and respiratory syncytial virus (RSV) vaccines.

We are particularly keen to have your input, as an organisation that [INSERT TEXT ON REASON FOR INVITATION].

This workshop is part of I-Consent, a European Union Horizon 2020 research project which seeks to investigate and address existing challenges and barriers to informed consent for vaccine trials.

Informed consent is absolutely crucial from an ethical and legal perspective. Members of the public must be able to understand the research in which they are taking part, but this is hindered by cumbersome, bureaucratic and legalistic informed consent processes.

The I-Consent consortium involves eight partners from four European countries including academic, public health, medical and commercial institutions.

Meningitis Research Foundation's main role is to gather and present the perspectives of 6-10 patient associations from across Europe in an interactive workshop.

Topics of discussion may include:

- Comprehension of patient information
- Issues surrounding children's involvement in vaccine trials
- Fairness in regard to compensation/inducement for participation
- Patient expectation and feedback of research results

The objective will be to reach consensus on priority of issues in terms of their importance and difficulty, and explore potential solutions, identifying how informed consent procedures can be improved.

Prior to the workshop, we will ask you to complete a short pre-read exercise to familiarise yourself with the issues and to inspire discussion during the workshop.

The workshop will be held in London in **March 2018**, and all associated expenses (including standard class travel and accommodation) will be paid.

If you are interested in contributing to improved patient involvement in vaccine trials against severe infectious diseases, please contact Rosanna Russell on (+44) 333 405 6260 or rosannar@meningitis.org.

We look forward to hearing from you.
Yours sincerely,

Linda Glennie
Head of Research, Evidence and Policy
Meningitis Research Foundation

Website Twitter

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Annex 2: Pre-read exercise

I-Consent Workshop

Pre-read exercise

Consortium partners:

The I-Consent workshop is part of a European Union Horizon 2020 research project. The project aims to develop comprehensive guidelines that will improve the way scientists get informed consent from patients for participation in research. The workshop supports this aim by gathering feedback and perspectives from patient groups.

During the workshop, you will be asked to draw upon your experience as a patient group representative to identify issues and challenges relating to informed consent for vaccine trials. The goal is to come to a consensus on the priority of issues you identify in terms of their importance and difficulty.

The slides in this presentation provide background reading to help you become familiar with ideas about informed consent and inspire discussion at the workshop. Please read this information before attending the workshop and answer the survey questions as a summary of responses will be discussed on the day.

Please view these slides as a 'slide show' as the presentation contains animations.

This should take about an hour.

What is Informed Consent?

Informed Consent is the process through which a person voluntarily agrees to participate in research, after being informed of everything she or he needs to know about the research. This includes any potential risks and benefits, information on why the research is taking place and what is expected from her/him. This empowers the person to make a rational and informed decision about participation.

This process typically occurs in two ways; through conversations with the clinical researcher and by providing the person with detailed information to read. The latter will typically take the form of a patient information sheet or booklet, aiming to describe the study in simple language, using non-technical terms and explaining the risks and benefits of participation.

Why is it necessary within research?

The informed consent process protects research participants from harm and enables them to make their own decisions about whether to take part in clinical research. However, in the past, the participation of individuals in clinical research was not always voluntary.

Laws governing the informed consent process have been set over the last 70 years, and now there are national and international guidelines. Ethical and legal obligations dictate the current informed consent requirements which are now considered fundamental within clinical research.

Now click here to watch a short video which summarises the informed consent process and then return to the presentation

Video clip URL: https://www.youtube.com/watch?v=yNYGJKIPb7Q&feature=youtu.be

Why is there a need for new guidelines on informed consent?

Recruiting volunteers to participate in clinical trials is a key element in the development of new vaccines and other medicines. However, many trials now fail to recruit enough people, which presents a barrier to the development of potentially life-saving vaccines and treatments.

In part, this is because the informed consent process has become highly regulated. Regulation is vital both ethically and legally, but it has resulted in very long and complex consent documents, full of technical and legal language. Not only does this discourage some participants from taking part, even those that do consent are often left with a limited understanding of the study.

Why have we invited patient groups to participate in this workshop?

As patient groups, you have a unique insight into the perspectives and concerns of the people you represent. Your expertise in a range of areas will enable a broader conversation around the issues of informed consent for clinical vaccine trials.

The workshop will provide you with the opportunity to contribute towards the development of European wide guidelines on informed consent and network with other patient group organisations.

During the workshop, the following themes will be explored within the context of Informed Consent:

Children's assent

Patient expectations

Gender

Comprehension

The following slides give an introduction to each of these themes.

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Children's assent

What is assent?

Assent is defined as the willingness to participate in research by persons who are too young to give informed consent but who are old enough to understand the study, its expected risks and possible benefits, and the activities expected of them as subjects

It's important to consider assent in vaccine trials because...

Although vaccines are always tested on adults first, it cannot be assumed that they will be safe for children. There is a **risk that children** could be **harmed** by medical interventions **only tested in adults.**

Many vaccines are **specifically designed** for use in **healthy children** and must be tested on children to ensure they are safe and effective for this age group.

The **age of consent for research** is written into law in **many European countries** and signifies when a child is deemed able to give informed consent.

This means that although **older children** are able to **understand a study**, they cannot legally give informed consent for themselves. In this case, the researcher is obliged to ask for the **child's assent.**

In these cases, **consent must come from the parent or guardian** although the views of the child must also be considered. This can cause complications if the views of both parties are not aligned.

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The age a person can legally give informed consent or assent to participate in research varies by country.

The table below displays the requirements within the five countries where the patient groups attending the I-Consent workshop are based.

Country	Legal age of consent	Age for giving assent	Number of required signatories
Italy	18 years	Case-by-case assessment	Both parents
Netherlands	16 years	12-15 years with own signature	Both parents
Republic of Ireland	16 years (for clinical trials), 18 years (for all other research)	Assent can be given from 7 years, or according to the capacity of the child	One parent
Spain	18 years	12-17 years with own signature	One parent
United Kingdom	16 years	Assent is not explicitly required. The explicit wish of a minor capable to form an opinion is considered by researcher	One parent

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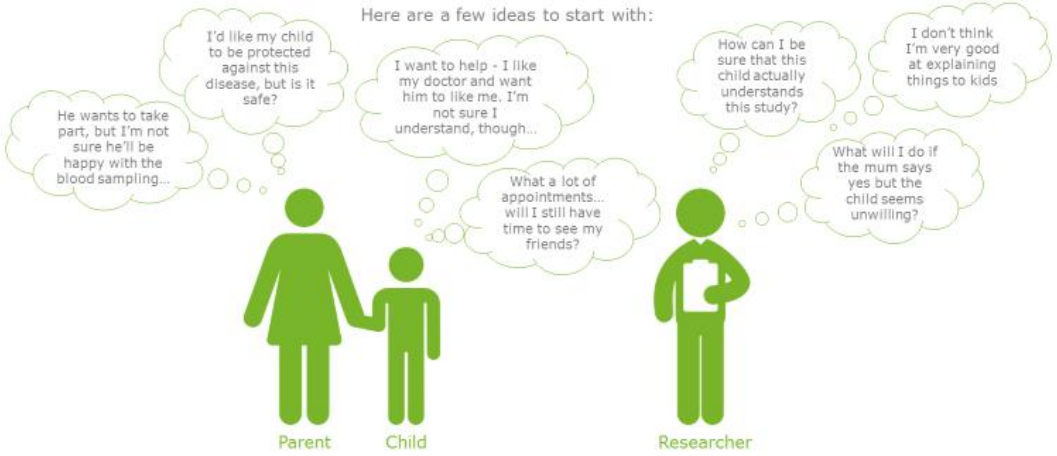
During the workshop, we're going to be discussing the following question:

What are the challenges of recruiting children to take part in vaccine trials?
Consider how the consent / assent process involves the child, parent and researcher.
What sorts of issues or concerns could each group have?

Please think about the question and write down any ideas you have ahead of the workshop

Here are a few ideas to start with:



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Patient expectations

It's important to consider patient expectations in vaccine trials because...

Patients may want to know how they **contributed** to the **outcomes of the research** and have **expectations regarding feedback** of the research findings including specific information about their health. This is often difficult, or impossible, to provide.

Sometimes a participant may have unrealistic expectations based on a misunderstanding of parts of the study.

In the case of some therapeutic trials (such as trials for cancer treatments), the patient may expect major health benefits, such as extended life expectancy or relief of symptoms.

In **vaccine trials**, the individual **risks** are relatively **low** but the perceived **immediate health benefits** to the individual may also be. Some parents will enrol children in a vaccine trial against a disease they fear, such as meningitis.

Therefore, the motivation to participate in a clinical vaccine trial may be more **altruistic** in terms of contributing to the health of society.

Financial inducement is considered **ethically unacceptable** as it may override true informed consent for people affected by poverty, or for older children and young people with limited judgement. As a result, any **financial rewards** must be limited to **compensation** for travel, time and inconvenience.

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During the workshop, we're going to be discussing the following question:

When deciding whether to take part in a vaccine trial, participants will have certain expectations. What might encourage them to take part and what might put them off?

Please consider the question and write down any ideas you have ahead of the workshop

Here are a few ideas to start with (both realistic and unrealistic):

Gender

It's important to consider gender in vaccine trials because...

Medicines and vaccines are routinely trialled in men, women and children to ensure they are **safe** and **effective** within the specific group they have been designed for.

However, until recently **pregnant women** have been **excluded** from clinical trials to avoid the additional legal complexities around safeguarding the unborn child. For the same reason, women participating in clinical trials are **required to take contraceptives** and may be asked to provide **pregnancy tests** throughout the course of the study. These contraception requirements are often **out of proportion** to the actual **risks of a study**.

As more vaccines are being developed specifically **for pregnant women in order to protect newborn babies**, **vaccines** increasingly **need to be tested in this group**. Usually, consent to these trials is only required from the pregnant woman herself. Some people believe that if there is a significant **chance of benefit or harm to the foetus, consent from the father should also be obtained**. Others argue that this could interfere with a woman's right to make independent decisions about her healthcare.

Similarly, the Human Papilloma Virus (HPV) vaccine for preventing cervical cancer was tested on girls as they are the priority target.

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During the workshop, we're going to be discussing the following question;

What might different genders consider when providing informed consent?

Please consider the question and write down any ideas you have ahead of the workshop. In may also help to ask a member of the opposite sex for their views.

Comprehension

It's important to consider comprehension in vaccine trials because...

The **informed consent documentation** used for clinical trials has become **tightly regulated** and **highly legalistic**

This has led to the introduction of **longer** and **more complicated consent documents**, incorporating technical and legal language, making them less likely to be read or understood.

As a result participants often have a **limited understanding** of **study information** even when they have signed a consent form. Decisions around participation may be driven more by trust in the doctor or by a deference to authority than by the information provided.

In addition, informed consent documents are usually developed by medical professionals / researchers whose focus is on **what information** needs to be **presented**, rather than **how.**

Physicians tend to receive **little training** on how to **communicate** with participants and often **misinterpret the requirements** and legal standards of informed consent themselves.

For optional further reading, please see Christine Grady, at el. (2017) Informed Consent, *The New England Journal of Medicine*; 376:856-867, accessible here: http://www.nejm.org/doi/full/10.1056/NEJMra1603773

How can comprehension levels be improved?

Comprehension tests

It has been suggested that participants' understanding of a trial should be tested to ensure that their informed consent is valid. But how should this best be done? And how might this affect participation?

Interactive and/or Digital Informed Consent Documents

Information technologies, such as apps, tablets and smartphones, could help modernise and improve the informed consent process. Information could be presented in more engaging ways through the use of creative graphics or interacting with participants via online discussions.

This approach could also provide a way of assessing patient's understanding of the process on an ongoing basis.

In theory, these technologies should allow for an improved informed consent process. However, the drawbacks of using digital tools should also be considered – including how they might help or hinder the researcher in ensuring that information is important and relevant. Interactions need to be brief, engaging, and informative about risks and benefits in a way that users can easily appreciate. There is also a risk that those who are less tech savvy or who do not have a smartphone will be excluded from participation.

During the workshop, we're going to be discussing the following question:

What features of the informed consent process may make it difficult to understand?

Please consider the question and write down any ideas you have ahead of the workshop

Here are a few ideas to start with:

We'd now like to show you a real-life example of a patient information sheet which you can access here.

Please read the patient information sheet in full. This should take approximately 20 minutes.

After reading this document, we'd like you to complete a survey to provide feedback on comprehension levels. This should take approximately 15 minutes.

Click here to begin the survey.

Please note that the findings of this survey will be presented during the workshop to introduce our discussions about the informed consent process. The findings will be aggregated and your responses will remain anonymous.

Patient information sheet URL: http://www.meningitis.org/getmedia/e525a70a-3233-4e44-a173-7ad271e2277b/OVG-Developing-vaccine-to-prevent-RSV
Survey URL: https://www.surveymonkey.co.uk/r/HBW2JQ3

You've now completed the pre-read task.

Thank you for your time. We look forward to seeing you at the workshop!

Annex 3: Example patient information document

Oxford Vaccine Group
University of Oxford
Centre for Clinical Vaccinology and Tropical Medicine,
Churchill Hospital, Headington, Oxford OX3 7LE
Telephone: 01865 611400 info@ovg.ox.ac.uk www.ovg.ox.ac.uk

Study information booklet

Developing a vaccine to prevent RSV, a cause of serious respiratory infections in infants

The Oxford Vaccine Group would like to invite your child to take part in a study to understand the safety of a new respiratory syncytial virus (RSV) vaccine.

This study is being run by the Oxford Vaccine Group in collaboration with Janssen, a pharmaceutical company of Johnson & Johnson who make vaccines. The overall aim is to develop a vaccine that prevents RSV disease.

The Oxford Vaccine Group is part of the University of Oxford and is an independent research team of doctors, nurses and play assistants. We carry out research studies of new and improved vaccines for babies, young children, teenagers and adults and teach doctors and nurses about immunisations. In the past 5 years alone, over 7000 participants in the Thames Valley area have taken part in our research studies.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully, and discuss with others if you wish. If anything is unclear or you would like further information, please contact the study team.

Thank you for reading this. You will be given a copy of this information to keep.

Summary

- We are researching a new vaccine against respiratory syncytial virus (RSV), a highly infectious respiratory (lung) illness which is a common cause of infection in infants and can cause serious acute illness, hospitalisation and in some cases death. Despite the high disease burden, no licensed vaccine is currently available for RSV.
- **What do we want to know?** – This study is researching a new vaccine called Ad26.RSV.preF. The main purpose of this study is to check that the vaccine is safe. We will also measure how your child's immune system responds to the study vaccine.
  - **How are we going to do it?** – Across the study twelve healthy adults and 36 children aged 12 to 24 months will take part. They will receive either the new vaccine Ad26.RSV.preF or placebo (a salt water injection). Participants will receive the study vaccine on 2 occasions, with 9 routine visits from a nurse or doctor, four blood tests and phone calls every 14 to 30 days over 1 year.
- Vaccines will be given at your home, and you will be provided with 24 hour contact details for a study doctor
- A description of this clinical trial (research study) will be available at http://www.ClinicalTrials.gov as required by laws governing our studies. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the study results. You can search this Web site at any time.

Why has my child been invited to take part?

You have been approached because your child is 12-24 months old and you live in an area where the study is being carried out. This booklet may have been posted to you by an NHS database. Please note that unless you have previously been in contact with us about this study, the Oxford Vaccine Group has not been given your child's name and address. Taking part in this study is voluntary and if you do not want your child to participate you do not have to reply to this invitation.

What is respiratory syncytial virus (RSV)?

Respiratory syncytial virus (RSV) is a highly infectious respiratory virus (germ) that infects the lungs and breathing passages. In children RSV infection typically occurs at least once a year and in adults every 3-5 years during the winter season. RSV is considered to be one of the most important causes of serious acute respiratory illness in infants and children under 5 years of age. Children usually experience mild to moderate cold-like symptoms and recover in a few days to a week. However, some infants require hospital admission and sometimes need a ventilator to help with breathing. In a small number of these cases, RSV can result in death. RSV disease is also associated with persistent coughing and recurrent wheeze. Despite the high disease burden, no licensed vaccine is available for RSV.

What are we studying?

In this study, we are interested in learning more about an investigational vaccine designed to protect against RSV disease. Investigational means that the study vaccine is not yet licensed for use in the UK or elsewhere.

Vaccines stimulate our immune system to help protect against infections. If a child or an adult comes into contact with an infectious disease against which they have been vaccinated (or "immunised"), their body will be able to recognise and fight the disease. This is known as an **immune response.** Without vaccines, people are at increased risk of catching many serious diseases.

We are interested in studying a new vaccine, Ad26.RSV.preF. The main purpose of this study is to see if the study vaccine is safe (if it causes any side effects) and how people feel after the vaccine ('tolerability'). We will also measure your child's body's immune response to the study vaccine. In this study, some participants (adults and toddlers) will receive placebo instead of the study vaccine. Placebo given in this study will consist of sterile saline for injection, with no vaccine in it.

The **Ad26.RSV.preF vaccine** is made from a virus called Adenovirus. This virus is common in everyday life and can cause colds and respiratory infections. However, the adenovirus used in this study vaccine has been weakened so that it cannot multiply and cause a respiratory infection and therefore is expected to be harmless to humans. The vaccine includes certain parts of the DNA from the RSV virus. DNA is a natural substance found in all living things, including people and viruses. When the study vaccine is injected, the vaccine will tell the body to make small amounts of a protein normally made by RSV. We will then see if your child's body develops an immune responses to these RSV proteins using blood tests. This is the first time that Ad26.RSV.preF will be given to children, however this vaccine has been given to 48 adults over 65 years in a previous study. This study raised no safety concerns. In addition to this the vaccine will be given to 12 more adults at the start of this study.

In the 1960s different vaccines in which the whole RSV virus was chemically inactivated were developed. These induced an inappropriate immune response in infants without pre-existing immune antibodies (seronegative) and increased the severity of the RSV respiratory disease in these infants instead of protecting them. This was not observed with vaccines based on live, but weakened, -versions of the RSV virus, suggesting this problem is not seen with all RSV vaccines. The data in animals immunised with the Ad26.RSV.preF vaccine being used in this study are reassuring, showing an appropriate immune response and protection against disease. As part of this study your child will be closely monitored for respiratory infections.

Who can take part in the study?

The study will take place over three sites in the UK (Oxford, Manchester and Southampton). A total of 36 children and 12 adults will be enrolled in Europe.

We want to recruit children who:

- Are 12-24 months of age
- were not born premature (before 37 weeks gestation) or below 2.5kg
- Have received their routine vaccinations
- Are in good health without any significant medical illness
- Have previously had an RSV infection (e.g. a cough, cold or bronchiolitis). This will be most children aged 12 to 24 months, but will be confirmed by a fingerprick blood sample checking whether your child is RSV 'seropositive'.

What happens in the study?

The study consists of:

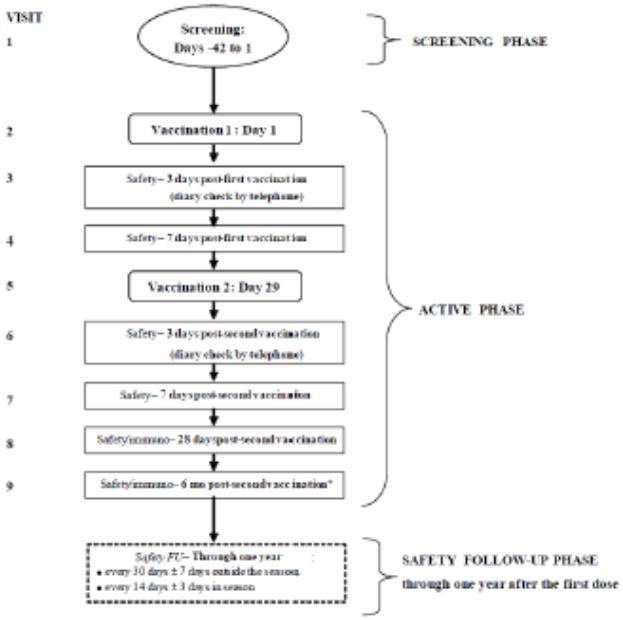
- Vaccination with 2 doses of Ad26.RSV.preF or placebo 1 month apart
- Blood tests and nose swabs
- Completion of a symptom diary for 7 days following vaccination

- 7-9 visits at home over a 30-week period, and regular phone calls
- We will also ask your permission to access information about the mother's vaccination through medical notes.

In this study, your child would be randomly allocated to receive either Ad26.RSV.preF or placebo by chance (like flipping a coin). This is a double-blind study which means that neither you nor the Study Doctors and clinical staff (apart from those who administer the study vaccine) will know whether your child has received the study vaccine or placebo. In an emergency your study doctor will be able to find out which treatment your child has received.

You or the study team would not be able to influence which vaccine your child is given and you would not be told what your child had received until after the end of the study.

The study design is shown below.



*If Visit 9 occurs during the RSV season, an additional visit will be made by telephone at the end of the RSV season to collect safety information

	Group	Day 1	Day 29/Week 4
12 Adults	Group 1	Ad26.RSV.preF ($1x10^{11}$ vp*)	Ad26.RSV.preF ($1x10^{11}$ vp*)
	Group 2	Placebo**	Placebo**
36 Children	Group 3	Ad26.RSV.preF ($5x10^{10}$ vp)	Ad26.RSV.preF ($5x10^{10}$ vp*)
	Group 4	Placebo**	Placebo**

*viral particles **Placebo is normal saline

Other things that will happen during the study are listed below:

Information

Collection of information about your child such as medical history and details of any medications they are currently taking or have taken in the past.

Vital signs

The study doctor will measure your child's height, body weight, heart rate, breathing rate and body temperature. The study doctor will also conduct a physical examination and general health check during the study.

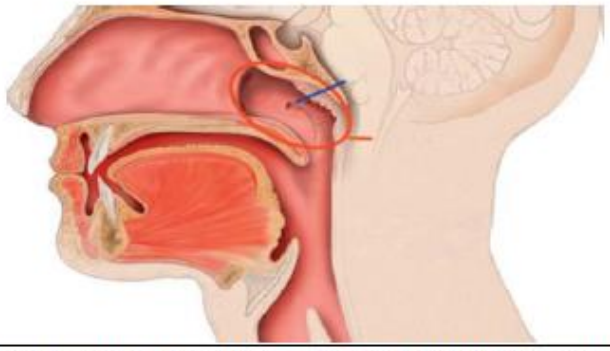
Blood tests

In order to understand the effect of the vaccines, your child will have 4 blood tests through the study. The first blood test will be to assess your child's antibodies against RSV (serostatus) and subsequent tests will be to determine your child's response to the vaccine. We will take up to 5ml (a teaspoon) of blood.

In order to minimize any distress caused by the procedure we will:
-Use anaesthetic cream to help numb the skin (provided before visits with explanation of use). This will not be used for 'fingerprick' blood tests.
-Provide a play assistant to be present at all blood test visits to help distract your child
-Only have a maximum of 2 attempts at obtaining the blood, and you would have final decision to proceed with 2nd attempt if 1st attempt was unsuccessful.

Nasal swab

If your child experiences respiratory symptoms, we will do a nose swab to test for the RSV virus. The swab will look like a cotton bud on a flexible wire. We will tilt your child's head back and then pass the swab towards the back of the nose and rotate it gently (area indicated on diagram below). This feels a bit tickly in the nose but will only take a few seconds.



Picture modified from: Shak, J.R., Vidal, J.E., & Klugman, K.P. 2013. Influence of bacterial interactions on pneumococcal colonization of the nasopharynx. Trends in Micro. 21:3 pp 129-135

Diary

Following vaccination we will ask you to complete a diary for 7 days in order to record any reactions following vaccination.

Review of study eligibility

Based upon your child's medical history and tests done during screening the study doctor will decide if your child can participate on the study. Should there be any abnormalities found during the screening process, these would be discussed with you and a recommendation to follow up with your child's GP would be made. With your agreement, we would also contact the GP to report any findings.

Medications

At each visit the study doctor/nurse will review your child's medications (if they are taking any) with you and ask you about any side effects.

How will your child receive the study vaccine?

If you decide for your child to take part in this study, you also agree that they receive the study vaccine as directed by the study staff.

The study vaccine is given via an injection. The needle is put into a muscle of their leg. This will be done 2 times during the study.

What are the side effects of any treatment received when taking part?

Potential Discomforts, Side Effects, and Risks Associated with Ad26.RSV.PreF Vaccine

The Ad26.RSV.PreF Vaccine has been studied in the laboratory and in animals. The active vaccine component of Ad26.RSV.preF vaccine has also been administered once in an ongoing clinical trial to a total of 48 persons greater than 60 years of age and has been shown to be generally safe and well tolerated. Vaccines similar to the Ad26.RSV.PreF Vaccine have been administered to a limited number of human volunteers in clinical trials of vaccines designed to prevent RSV and other diseases including HIV (Human Immunodeficiency Virus infections), Ebola and Malaria. These vaccines have been shown to be generally safe and well tolerated.

Local symptoms at the injection site (moderate injection site pain and tenderness, and moderate to severe redness at the injection site) and body symptoms (headache, chills, joint pain, muscle pain, tiredness/generally not feeling well/fatigue and fever) have been previously seen with the HIV, Ebola and Malaria Ad26 vaccines.

In two recently completed clinical trials, 59 volunteers received 70 doses of an earlier version of the RSV vaccine (Ad26.RSV.FA2). This vaccine was very similar to the current version (Ad26.RSV.PreF) vaccine used in this trial. The only reported local symptom was injection site pain (mild to moderate) except for one case of mild swelling. The reported body symptoms were mostly mild to moderate. Those more frequently seen following Ad26.RSV.FA2 compared to placebo were chills, headache, tiredness/generally not feeling well/fatigue, joint pain, muscle pain and fever.

All vaccines can cause side effects. Problems that are not expected may arise and they may be life-threatening. If your child has any side effects or problems during your participation in this study, you should let your child's study doctor know right away. There may be risks with the use of Ad26.RSV.PreF vaccine that are not yet known. Sometimes during a study the sponsor may learn new facts about the study vaccine. It is possible that this information might make you change your mind about having your child in the study. If new information is discovered, your child's study doctor will tell you about it right away.

What are the possible benefits, disadvantages and risks of taking part?

Benefits

There is no known medical benefit to your child from being in the study. By taking part in the study your child may help future patients to prevent severe RSV.

Risks and possible side effects related with vaccination in general

General Risks Associated with Vaccination: There may be arm discomfort, pain or soreness around the injection, bruising, swelling or redness at the site of injection. These reactions may occur with all types of injections. It is also possible that your child will get a fever, chills, rash, aches and pains, muscle pain, nausea, headache, and fatigue (feeling tired). The side effects usually last 48 to 72 hours. Rarely, people may experience more severe side effects that limit their normal activities or make them go to the doctor.

It is rare, but your child could have an allergic reaction to a vaccine, including a rash, hives, or difficulty breathing, itching, and swelling of lips, tongue or face. **Allergic reactions can be life-threatening**; therefore, the study staff will watch your child for at least 30 minutes after each injection. You should tell your study doctor if your child has ever had a bad reaction to any injection or vaccine. The research doctors and nurses carry all necessary medication to treat serious allergic reactions. If you think your child is having a severe allergic reaction after your doctor or nurse leaves, contact the emergency number and seek medical attention immediately.

Side effects from tests:

Blood tests: Taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.

Nasal swab: Your child may experience some slight discomfort or tickling in the nose while this procedure is being done.

Before participating you should consider if this will affect any insurance you have for your child (e.g. travel insurance, private medical insurance) and seek advice if necessary.

Will I be compensated for travel and inconvenience?

You will not be paid to participate in the study. However for where home visits are not possible we will reimburse travel costs and inconvenience up to a maximum of £45.00 per visit.

If you wish to take part

If you are interested in your child taking part, a member of the study team will discuss the study with you in more detail via the telephone. We will then arrange an appointment to meet you at your home, at your convenience, to answer any further questions that you may have, check your child's health and

complete the consent form if you wish to proceed with the study. The first appointment should last around one and a half hours, and all following appointments between 30-45 minutes.

You will also have 24hr telephone access to a study doctor should you have concerns relating to the study. We will let your GP, health visitor and child health department know that your child is taking part in the study.

What are the alternatives to taking part in this study?

Taking part in this research is completely voluntary and if you decide to say no it will not affect your child's regular care in any way. Your child does not have to be in this research study. You are also free to change your mind and withdraw your child at any time without giving an explanation. It will not affect your child from getting all the care, medicine, and equipment they should be getting.

What will happen to any samples my child gives?

Samples are any fluid (e.g., blood, nasal secretions) collected from your child in this study. The samples we take for this study will be labelled with a study number and tested anonymously in certified laboratories. Your child's samples may also be shared with research partners for scientific research purposes. Before sharing with research partners, your child's samples will be labeled with a code number that is different from your study number. Your child's samples will not contain any personal identifiers. Some or all of your child's samples may also be kept and used for up to 15 years. This will allow for the scientific research described above to be done in the future as new discoveries are made. Samples may be transferred outside of the UK and EU for tests from labs with specific experience. The sponsor will ensure that your samples are kept securely. Your child's samples will be destroyed no later than 15 years. You will not be informed when they are destroyed.

You can withdraw your permission for your child's samples to be used for future research. In this case your child's samples will be destroyed only after they are no longer needed for the main study. You would need to tell your child's study doctor that you are withdrawing your consent for your child's samples to be used for future research. This can be done at any time, for any reason.

Your child will not be paid for any use of the samples, results, or inventions made from research on them. You are providing your child's samples for use by the sponsor. The sponsor (and research partners, where applicable) plan(s) to own the use of the results, treatments, or inventions that can be made from this research.

What happens when the study stops or if my child stops the study early?

Once all participants within the study have completed their relevant visits the study will continue for several months for the analysis and interpretation of the findings. Once complete, a publication will be written and published. Following this, we will notify you of the results and provide a link to the published paper. This whole process can take anywhere from one to three years after completion of all study visits. All publications arising from our studies are listed on the Oxford Vaccine Group website.

Your child's study doctor has the right to take your child out of the study at any time with or without your agreement. The sponsor has the right to direct your child's study doctor to take your child out of the study at any time with or without your agreement. These decisions will be made if:

- It is in your child's best medical interest to stop their participation
- Your child needs treatment not allowed in this study
- Instructions are not being followed for your child's participation in the study
- The study is cancelled

If your child stops the study early, we would ask to arrange a visit as soon as possible to have final tests done. Blood samples for safety laboratory and immune response testing may be collected. Also, a nasal turbinate for immune testing may be collected as well if the early exit is within 14 days of the previous vaccination.

If your child stops the study early, his/her blood samples will continue to be analyzed as described in this form unless you specifically ask for his/her samples to be destroyed. This is to protect the quality of the study. The study doctor will contact you 6 months after your child's last dose of study vaccine. He/she will ask if there were any side effects. This information will be added to your child's study record. The sponsor will not collect any new information from your child.

What if relevant new information becomes available?

Sometimes we get new information about the study vaccine that might be relevant to this study. There may be risks with the use of Ad26.RSV.PreF Vaccine that are not yet known. If that happens or if the study is stopped for any reason, we will discuss it with you as soon as possible as this information might make you change your mind about your child being in the study. We will write to your GP with information about you and your child's continuing care. If your child stops the study early, you agree not to limit our use of your child's study information.

What if there is a problem?

If you feel that your child has been injured or has become ill as a result of your child's participation in the study, immediately contact your child's study doctor.

The Sponsor will provide compensation for injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that the Sponsor should compensate your child without you having to prove that it is their fault or go to court.

The Sponsor will pay compensation where the injury is serious and persistent and probably resulted from:

- A drug being tested or administered as part of the study protocol;
- Any test or procedure your child received as part of the study that your child would not have undergone but for taking part in the study.

The Sponsor has agreed to be bound by the ABPI guidelines. (Please ask if you wish more information on this or go to the ABPI website at www.abpi.org.uk)

The Sponsor will not pay the costs to test or treat a condition or injury that is not related to the study drug, or study procedure, or for expenses related to the normal progression of a pre-existing medical condition or an underlying disease. In no event will the Sponsor pay for treatment for injury or illness that is not a result of the study.

The Sponsor will maintain insurance for clinical research as required by local law and regulations.

To help avoid injury, it is very important to follow all study directions.
The above statements do not limit your child's legal rights.

What if I wish to complain?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the Oxford Vaccine Group on 01865 611400 or email info@ovg.ox.ac.uk. You can also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email the head of CTRG, Heather House ctrg@admin.ox.ac.uk.

Will my child's taking part in this study be kept confidential?

The Sponsor will use the information collected about your child for the purposes of the study and for scientific research. The Sponsor may also use this information to apply for permission to sell the vaccine in some countries. The information will be stored both on paper and on computer, without identifying your child by name. To protect your child's privacy, the information will be labelled with a code number. If the results of the study are published, your child's identity will be kept confidential. By signing this form, you are permitting this use of your child's information.

The study doctor will keep your child's personal medical records and a list that links your child's name to their code number for at least 15 years.

Regulatory authorities, NHS R&D department representatives, employees at the study site and representatives of the Sponsor will be able to access this list in order to compare and check the study information collected about your child with information in your child's medical records. As far as the law allows, your child's medical records will not be made public. By signing this form, you are allowing direct access to your child's medical records by those who have legitimate reason to look at them.

The information collected may be sent to other members of the Sponsor's group of companies, to contractors working for them and to regulatory authorities. None of this information will contain your child's name. It may also be sent to some countries outside Europe that may not have the same level of data privacy protection as Europe. The Sponsor will protect your child's privacy as far as the law allows and will keep and supervise the information collected about your child only for as long as needed.

You can arrange with the study doctor to see the information collected about your child, and you can ask for any mistakes to be corrected. If your child leaves the study at any time, the Sponsor may still use your child's information collected up to that point, as the law allows.

Involvement of the General Practitioner/Family Doctor (GP)

We would like your permission to contact the doctors your child sees regularly (GP) to let them know that your child is taking part in this study. It is important for all your child's doctors to know that your

child may be receiving an investigational vaccine. We may also need to contact your child's GP to request their vaccination history and medical history to check if they meet our inclusion/exclusion criteria for the study.

Who is funding the research?

Janssen Vaccines & Prevention B.V, a pharmaceutical company Represented by in the UK by Global Clinical Operations UK, Janssen Research & Development
50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4DP

A pharmaceutical company that makes vaccines are funding the Oxford Vaccine Group to undertake this research. The study investigators do not have financial conflicts of interests with the study funder.

Who has reviewed this study?

All clinical research is looked at by an independent group of people, called a Research Ethics Committee to protect your child's safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by South Central Berkshire Research Ethics Committee.

What do I do now?

You do not need to make a final decision straight away. Please contact us by:

Tel: 01865 611400
Email: info@ovg.ox.ac.uk
Website: http://trials.ovg.ox.ac.uk/trials/rsv-vaccine

Members of the research team will be happy to discuss the study with you and answer any questions you may have. Alternatively, you can complete the reply slip and return it in the pre-paid envelope provided. You are welcome to tick the 'No' box below and provide feedback if you wish.

A postcard reminder would be posted to you in two weeks' time. If we do not hear from you after this, we will assume that you do not want to take part in the study. If you do not wish to receive invitations of this kind in the future, please contact the NIHR CRN: Thames Valley and South Midlands – Primary Care team on:
Email: optout.tvsm@nihr.ac.uk, Phone: 01865 223295
Address:
Optout TVSM
NIHR Clinical Research Network: Thames Valley & South Midlands
TVCN Offices, Block-8
Nuffield Orthopaedic Centre
Windmill Road
Headington
Oxford OX3 7HE

Please provide your child's full name, date of birth and postcode, if you do not provide all data it is difficult to ensure you are removed from future mail outs. Postcard reminders are sent two weeks after the initial invitation. There is a possibility that your response and the postcard reminder may cross in the post. We apologise if this is the case.

Contact

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital Oxford OX3 7LE
Tel: 01865 611400
Email: info@ovg.ox.ac.uk
Website: http://trials.ovg.ox.ac.uk/trials/rsv-vaccine

Oxford Vaccine Group
University of Oxford
Centre for Clinical Vaccinology and Tropical Medicine,
Churchill Hospital, Headington, Oxford OX3 7LE
Telephone: 01865 611400 info@ovg.ox.ac.uk www.ovg.ox.ac.uk

Parent/Legal Guardian Consent Form

Short Title: Developing a vaccine to prevent RSV, a cause of serious respiratory infections in infants

Study Title: A Randomized, Double-blind, Phase 1/2a Study to Evaluate the Safety, Tolerability and Immunogenicity of Ad26.RSV.preF in Adults 18 to 50 Years of Age and RSV-Seropositive Toddlers 12 to 24 Months of Age

Principal Investigator: Dr Matthew Snape

Child's name:		CRF ID:	
Parent/Legal Guardian's name:			

	Please read the following statements and put your initials in the box to show that you have read and understood them and that you agree with them.	Please initial each box
1	I confirm that I have read and understand the information sheet dated 23 Nov 2017 for the above study. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.	
2	I understand that my child's involvement is voluntary and that I am free to withdraw my child at any time, without giving any reason and without my child's medical care or legal rights being affected.	
3	I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals from the Sponsor or authorised by the Sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records.	
4	I agree to my child's GP being informed of my child's participation in the study. *(Your child may still be able to take part in this study even if you do not agree to this.)*	
	OPTIONAL: I agree that my child's samples can be used for future research.	
	OPTIONAL: I agree to being contacted by the Oxford Vaccine Group about studies in the future that are related to this study and I understand that I would be under no obligation to take part in these future studies	

To be filled in by the parent/legal guardian

I agree for my child to take part in the above research study

Your name	**Date** (Day/Month/Year) (e.g. 01 Jan 2016)	**Signature**

To be filled in by the person obtaining consent (investigator)

I confirm that I have explained the nature, purposes and possible effects of the research study to the person whose name is printed above. They have agreed for their child to take part by signing and dating above.

Name of Investigator (or person obtaining consent if different from Investigator)	**Date** (Day/Month/Year) (e.g. 01 Jan 2016)	**Signature**

Instructions to Study Staff

If the study doctor signing this form is not the Principal Investigator, they must be authorised to take consent on the Site Signature (Delegation) Log.

Filing instructions:

- 1 (copy) for parent/legal guardian
- 1 (copy) for medical notes
- 1 (original) to be filed in the Trial Centre File

Annex 4: Participant ranking sheet

What features of the informed consent process may make it difficult to understand?

Assign a score with the highest being the most important and lowest being the least important

Ref.	Issues	Score
A		
B		
C		
D		
E		
F		
G		
H		

Annex 5: Workshop agenda

Time	Focus	Summary	Presented by
9:00 (10 minutes)	Welcome and introductions	Welcome and introduction to the I-Consent project and workshop organisers.	Workshop facilitator and Meningitis Research Foundation
9:10 (5 minutes)	Participant introductions	Brief introductions by each participant stating name and organisation as participants will have already met each other and the organisers the evening prior to the workshop.	Each participant in turn
9:15 (15 minutes)	Workshop overview	An overview of the aims, format and agenda of the workshop, followed by a short PowerPoint presentation to provide a basic overview of informed consent.	Workshop facilitator
9:30 (10 minutes)	Theme 1: Comprehension (pre-read survey findings)	Survey findings will be aggregated, without reference to individual responses. They will be presented to demonstrate issues in terms of comprehension within the informed consent process.	Workshop facilitator
9:40am (80 minutes - 10 minutes extra to get used to the format)	Theme 1: Comprehension theme (nominal group)	Use the Nominal Group Technique to explore issues around the theme of comprehension.	Workshop facilitator
11:00 (20 minutes)	Coffee break	This break will be used by the workshop organisers to combine the ranking sheets from theme 1.	-
11:20 (70 minutes)	Theme 2: Patient expectations (nominal group)	Use the Nominal Group Technique to explore issues around the theme of expectations and compensation.	Workshop facilitator
12:30 (60 minutes)	Lunch	This break will be used by the workshop organisers to combine the ranking sheets for theme 2.	-
13:30 (70 minutes)	Theme 3: Assent (nominal group)	Use the Nominal Group Technique to explore issues around the theme of assent.	Workshop facilitator

14:40 (20 minutes)	Coffee break	This break will be used by the workshop organisers to combine the ranking sheets from theme 3.	-
15:00 (70 minutes)	Theme 4: Gender (nominal group)	Summary: Use the Nominal Group Technique to explore issues around the theme of gender.	Workshop facilitator
16:10 (10 minutes)	Short coffee break	This break will be used by the workshop organisers to combine the ranking sheets from the expectations and compensation theme exercise and pull together concluding remarks.	-
16:20 (20 minutes)	Conclusions and feedback: ranking stage (part 2)	Present the combined scores from the ranking stage back to the group, highlighting the key issues within each theme. Participants will then be given the opportunity to alter the order of priorities if desired.	Workshop facilitator
16:40 (20 minutes)	Closing comments	Outline the next steps including the circulation of the topline findings the following week to ensure that the interpretation of consensus is accurate. The report will be circulated after publication. The facilitator will then thank the patient groups for their time / participation.	Workshop facilitator
17:00	Workshop ends		

Annex 6: Full list of issues groups by sub-theme within theme 1 (comprehension)

Question: What features of the informed consent process may make it difficult to understand?

Sub-theme: Why (should I take part) (combined score: 65)

- Give me why
- Tell me how many are affected
- Use a patient story to remind people of what it is
- It is difficult to understand why/could I participate in a study about a new vaccine. It seems important for the pharmaceutical company, not for me - my child is healthy
- The proposal is not interesting for the parents
- In the document there is no financial and ethical support for a parent who chooses to have his child in the experiment with the relative risk
- No known medical benefit *(in reference to page 7 of the example IC document)*
- Give me one good reason why I should participate
- Parents - give me a reason to care in the study. Something that makes sense
- Decisions may involve emotions

Sub-theme: Content clarity (combined score: 63)

- Explain vaccine aspects - ingredients, how it works, the after effects
- Bring balance in benefits and risks - benefits (none), risks (many)
- Technical/legal language
- High level of English to understand medical jargon
- What is Ad26.RSV.PreF? What does that mean?
- Benefit - maybe. Risk - may be life threatening
- No recognition of child and parent as different individuals and what that means for consent
- Protection of personal data, confidentiality
- Missing - who introduced this study to you?
- Clarity over: confidentiality, security of data, withdrawal process
- Unclear exactly what's required of the participant - needs summary
- What if you want to stop? What if you want to be deleted? It's not clear
- Ensuring real understanding before decision to/not participate
- I think it is not a problem of language but of substance of the proposal, no balance
- Long, complicated documents to explain the trial
- Comprehension of scientific/medical jargon/language
- Less opportunity for parent, real risk for child
- Problem: no refund. For problem about vaccination

Sub-theme: Format of presentation (combined score: 54)

- Small print
- Lay versions

- Accessibility for all – written/podcasts/other formats?
- Shorter, less technical text and use of images
- Information must be simple
- FAQ?
- Missing a flow chart
- Length of the document - too many pages, too much information unnecessary
- Order: ethical approval at the end. Why have I been asked to take part too late?
- Keep I/we/you pure
- Online I-Consent - adapt to new technologies
- Simple is clear and concise
- Informed consent current model sounds like an insurance proposal

Sub-theme: Tailored to audience (combined score: 47)

- If only verbal info is given the participant may not retain/recall this
- Law refers to 'average man'

Sub-theme: Relationship researcher and patient (combined score: 47)

- Participants may not feel able to ask questions to clarify their understanding
- More informed consent is formed between doctors and patients
- Pressure from researcher or health professionals

Sub-theme: Decision making (combined score: 41)

- Don't put all your hope on a document

Sub-theme: Model (combined score: 39)

- Informed consent - needs a better model
- We need to identify, list and prioritise patient concerns with the current 'informed consent' model

Sub-theme: Sponsor perceptions (combined score: 27)

- Influence of the pharmaceutical industry
- Can pharma be rehabilitated?

Sub-theme: Bias (combined score: 22)

- Do members of this group have any bias regarding informed consent?

Annex 7: Full list of issues groups by sub-theme within theme 2 (patient expectations)

Question: When deciding whether to take part in a vaccine trial, participants will have certain expectations. What might what might put them off?

Factors encouraging participation in a vaccine trial

Relationships and understanding (combined score: 113)

- Good trustworthy information
- I can / I want - is the question
- Encouraged or feel forced to participate
- Storytelling about choice, with good and bad results
- Motivator: more likely to take part if recommended by people I trust (doctor, patient group, my midwife, etc.)
- Motivator - clear understanding of exactly what is involved from start to finish
- Yes: good storytelling of doctor

Protection/efficacy (combined score: 100)

- Expensive vaccines for free (families with 2 or 3 children)
- Opportunity to get vaccinated
- Put off: unsure of potential benefit to me / others
- Protection for my child from illness
- Motivator: potential benefit for me / my child

Disease awareness (combined score: 96)

- Direct protection from a serious illness
- Motivator: more likely to take part if someone I know suffered from X

Economic compensation (combined score: 95)

- Economic compensation for risk
- How much time will this take? Costs, etc.
- Economic compensation
- Put off: costs of involvement - time, effect, expenses

Benefits to society (combined score: 90)

- Motivator: altruism, for the greater good
- The value of the study, to future generations
- Contribution to public health
- Thinking about future children
- High level of acceptance of vaccine and its value to society
- If the value/impact of the study won't be realised for a long time (timeline)

- After this trial, what will happen? All children will have this vaccine? (UK)
- I can demonstrate the benefit for humanity: for all children

Values/culture (combined score: 85)
- (Perceived) conflicts with values
- Relationship in the future: parents/own child - belongs to anti-vaccine groups
- Different choice between same couple conflict

Increased access to healthcare professionals (combined score: 76)
- Extra care/access to health professional
- Increased access to health professionals

Media (combined score: 75)
- Good news about vaccine potential
- Motivator/put off: news articles

Presumptions (combined score: 70)
- A healthy child?

Time/effort (combined score: 69)
- No: too much time involved

Patient/parent concerns (combined score: 53)
- No: don't want to hurt the child - extra injections
- Pain/harm to child - injections, blood tests, etc.

Infrequent but significant risks (combined score: 42)
- I can demonstrate the safety of vaccine tested
- What are the risks to my child? What is already known about safety?
- Potential anxiety for child's health for years/length of trial
- I can demonstrate low risk for patient

Placebo (combined score: 42)
- If my child gets/could get a placebo (no benefit to my child)
- Expectations - participants expect to be in treatment not placebo arm

Side effects (combined score: 40)
- Put off: uncertainty over safety/negative side effects
- Motivator: confidence in safety of vaccine, so no/minimal risk of adverse effects
- After-effects unknown
- Health security V negative health impacts
- No: scared for side-effects (Wakefield's influence)

Anti-vaccine lobbyists (combined score: 26)

- High level of refusals to vaccinate and how it can change society (negatively)
- Bad news about vaccines effects

Negative perception of vaccines (combined score: 16)

- Negative rumours on vaccines
- Vaccines are not effective
- No vaccines are not good for the immune system
- Vaccines are not 100% safe and effective
- There are already too many vaccines

<u>Factors discouraging participation in a vaccine trial</u>

Negative perception of vaccines (combined score: 122)

- Negative rumours on vaccines
- Vaccines are not effective
- No vaccines are not good for the immune system
- Vaccines are not 100% safe and effective
- There are already too many vaccines

Anti-vaccine lobbyists (combined score: 106)

- High level of refusals to vaccinate and how it can change society (negatively)
- Bad news about vaccines effects

Infrequent but significant risks (combined score: 104)

- I can demonstrate the safety of vaccine tested
- What are the risks to my child? What is already known about safety?
- Potential anxiety for child's health for years / length of trial
- I can demonstrate low risk for patient

Values/culture (combined score: 94)

- (Perceived) conflicts with values
- Relationship in the future: parents/own child - belongs to anti-vaccine groups
- Different choice between same couple conflict

Media (combined score: 81)

- Good news about vaccine potential
- Motivator/put off - news articles

Patient/parent concerns (combined score: 80)

- No: don't want to hurt the child - extra injections
- Pain/harm to child - injections, blood tests, etc.

Side effects (combined score: 73)

- Put off: uncertainty over safety/negative side effects
- Motivator: confidence in safety of vaccine, so no/minimal risk of adverse effects
- After-effects unknown
- Health security V negative health impacts
- No: scared for side-effects (Wakefield's influence)

Time/effort commitment (combined score: 68)

- No: too much time involved

Placebo (combined score: 59)

- If my child gets/could get a placebo (no benefit to my child)
- Expectations: participants expect to be in treatment not placebo arm

Presumptions (combined score: 54)

- A healthy child?

Relationships and understanding (combined score: 53)

- Good trustworthy information
- I can/I want - is the question
- Encouraged or feel forced to participate
- Storytelling about choice, with good and bad results
- Motivator: more likely to take part if recommended by people I trust (doctor, patient group, my midwife, etc.)
- Motivator: clear understanding of exactly what is involved from start to finish
- Yes: good storytelling of doctor

Disease awareness (combined score: 45)

- Direct protection from a serious illness
- Motivator: more likely to take part if someone I know suffered from X

Protection/efficacy (combined score: 43)

- Expensive vaccines for free (families with 2 or 3 children)
- Opportunity to get vaccinated
- Put off: unsure of potential benefit to me / others
- Protection for my child from illness
- Motivator: potential benefit for me / my child

Economic compensation (combined score: 42)

- Economic compensation for risk
- How much time will this take? Costs, etc.?
- Economic compensation
- Put off: costs of involvement - time, effect, expenses

Benefits to society (combined score: 34)

- Motivator: altruism, the greater good
- The value of the study to future generations
- Contribution to public health
- Thinking about future children
- High level of acceptance of vaccine and its value to society
- If the value / impact of the study won't be realised for a long time (timeline)
- After this trial, what will happen? All children will have this vaccine? (UK)
- I can demonstrate the benefit for humanity! For all child

Increased access to healthcare professionals (combined score: 30)

- Extra care / access to health professional
- Increased access to health professionals

Annex 8: Full list of issues groups by sub-theme within theme 3 (assent)

Question: What are the challenges of recruiting children to take part in vaccine trials? Consider how the consent / assent process involves the child, parent and researcher.

Testing understanding (combined score: 60)

- Space for child to ask questions, maybe with/without parents present if sensitive in nature
- Parents ask questions without child being present
- Ensuring parents/carers and child all fully cognisant of what's involved
- Researcher: Can I be sure that the child understands what will happen?
- Independent assessor? Test
- No direct decision by test subject
- Ensure child/parents/carers fully understand requirements, especially any potential negatives - not doing trial just to please doctor or parent
- Insurance for risk about the trials
- Parent: What are the benefits vs risks to my child?
- Some way of validating child's and parents understanding of trial/requirements
- Help economic for university study
- Child/parent: what if there are unforeseen consequences that affect future of child?

Family dynamics (combined score: 57)

- Problems if disagreements - especially if child wants to take part and a parent/carer doesn't want that
- Children: Depends on this personality/age. Might do it to please/to reject his parents
- Decision (at best): group decision
- The child doesn't take decision
- Child: parental 'pressure' to take part. Difficult to say 'no'
- Researcher: difficulty in dealing with differing views of parent and child
- The child is fragile - depends on their parents
- Strong parents = strong child
- Parents: one/both parents needed to consent?
- Parents: Time needed/balance other family commitments
- Researcher: different cultures/differing parent and child relationship

Communication (combined score: 53)

- Does not say why the subject is being asked. Does mention they are used to treatment *(in relation to the scene setter video)*
- Important to have the opinion of the personal doctor, family doctor
- Different levels of information required depending on age of child and complexity of trial
- Communicating why it is important. What do children need to know?
- Illustrate to the child and parents, the opportunity and the risk
- To move in the world of a child - be at the same level

- Be honest
- Time path to oversee parents and child
- Researcher - Can I use appropriate language to communicate with both the parents and the child?
- Speak about the after effect
- Creating appropriate/material informing them of trial
- Good relationship with medical doctor/researchers and parents
- Respect the age of the child
- Long list of questions to fill in - do they manage or are they in the mood
- It is important that child is informed by parent the first time
- Social media and images tailored to the child appropriate groups
- Give the feeling of being a team: researcher/child/parents
- E-mail app with the researcher: use of social media

Impact on daily life (combined score: 38)

- Children: physical after-effects (pain)
- Change of habits concern

Emotional response (combined score: 36)

- It is important to have in consideration the feeling of the child: worry and expectation
- Parent: doubts when taking the decisions (am I doing right?)

Friendships (combined score: 36)

- Child: I want to do this, but what will my friends think?
- Child: Might say no because of its classmates (afraid not to be understood)
- Child: Might say yes because of its classmates (proud to participate in the trial)

Society (combined score: 24)

- Benefit for the health of the world
- Important for trials: final decision with the parents

Change in circumstances (combined score: 20)

- Researcher: what if the child/teen decides to interrupt the process

Annex 9: Full list of issues groups by sub-theme within theme 4 (gender)

Question: What might different genders consider when providing informed consent?

Communication (combined score: 59)

- Could be opportune that male and female are related to the same gender
- If mixed groups of young people are receiving information there should be opportunities for individuals to ask questions privately
- Why does she need consent for vaccination and not for receiving birth control (M+F)
- Female: how does hormones influence the effect
- Male: what is benefit for the pharmaceutical
- Would the parents (1 or 2) not wonder why Holly wants to speak to Dr alone?
- Male: how sure is it that there will be no HPV after vaccination. What does it prove?
- Invitation was for girls! Why were boys being invited? M+F *(This comment is in relation to the gender scene setter)*
- If Dr Blake was female would she have arranged this differently (M+F) *(This comment is in relation to the gender scene setter)*

Relationships (combined score: 55)

- Pregnant: important to have consensus of the partner
- One or more parents may not be aware of Holly receiving birth control. F+M How would they react to finding out?
- Would Holly ask both parents or her mother first? M+F
- Pregnant: Should I consider my partners opinion if he disagrees with me?
- Man: My wife does have a lower cultural background compared to mine. I fear she doesn't understand what she signed
- Woman: I will sign my daughter's trial despite my husband's disagreement/refusal. Only one signature needed
- Maternal/child vaccine - family/cultural dynamics may play a part in decision making

Decision making for children (combined score: 47)

- No needle in my beloved one if not necessary
- What about single parents? (If you need both)
- Always for IC trial need approval of the parents

Risks to mother/child (combined score: 45)

- Men may be more risk averse re vaccines for their partner/child if uncertain over risks/benefits
- Risks to baby for pregnant female
- Risks to both pregnant woman and baby
- Pregnant: risks for my baby? Do I understand? What if something happens?

Decision making in pregnancy (combined score: 40)

- Pregnant women: Consent needed from partner? Communication with partner/researcher
- Consent needed from father of baby

Practicalities (combined score: 38)

- Male and female are different
- Different sensibility
- Practicalities of appointments/side effects - burden of whichever parent is more available to do these (usually mum)

Assumptions based on gender (combined score: 21)

- Assumptions based on gender/sex. Role VS Gender

Contraception/ trial (combined score: 19)

- Contraception during trial - is this/should this only be the responsibility of the woman?

Annex 10: Pre-read survey

Please note: correct answers to the first three questions, which test participants' comprehension of the IC document, are shown in green font.

Pre-read survey:

It's been suggested that comprehension tests should be introduced to ensure that participants' consent is truly informed. This may soon become a requirement for clinical research trials.

To give everyone an idea about what this could involve, we'd like all the workshop participants to try out this comprehension test.

1. Throughout the course of the trial, how many routine home visits will the participant receive from the nurse or doctor in total?

   5-7 visits over a 52-week period
   7-9 visits over a 52-week period
   7-9 visits over a 30-week period
   Don't know

2. What has been done to the Adenovirus used in this AD26.RSV.PreF vaccine to stop it causing colds and respiratory infections when the vaccine is injected?

   It has been killed so it cannot cause disease
   It has been weakened so that it cannot multiply
   It has been modified so it cannot use the human body's genes to make proteins
   It has been transformed into an inactive form of the RSV virus

3. Can participants find out whether they received the RSV vaccine or the placebo?

   Yes – anytime throughout the trial
   Yes – after the end of the trial
   No
   Don't know

We are now interested in understanding what you thought of this consent form.

For the purposes of these questions, please imagine that you are a participant considering whether or not to enrol your child in this study.

4. After reading the informed consent document could you make an informed decision on participation?

   Yes
   No

5. On a scale of 1 to 5, how helpful was the document in enabling you to understand what disease this vaccine might provide protection against?

   1 – Very unhelpful
   2
   3
   4
   5 - Very helpful

6. Page 6 explains the potential side effects that may be experienced when taking part in this trial. On a scale of 1 to 5, overall how helpful was this information?

   1 – Very unhelpful
   2
   3
   4
   5 – Very helpful

7. Would you know who to contact if your child suffered a mild adverse reaction?

   Yes
   No
   Don't know

8. Page 10 provides information about the confidentiality of data collected in the study. On a scale of 1 to 5, how easy or difficult did you find this information to understand?

   1 - Very difficult
   2
   3
   4
   5 - Very easy

9. If you met the recruitment criteria, how likely is it that you would enrol your child in this trial?

   1 – Very unlikely
   2
   3
   4
   5 – Very likely

10. If there anything else you would like to add please use the space below.