Minutes of public meeting of the PFAS Scientific Advisory Panel on Teams
10.00 – 11.30 am on Friday 4th August 2023

Panel Members present:	Dr Steve Hajioff – Independent Chair Dr Tony Fletcher – PFAS and Health member Prof Ian Cousins – PFAS and Environment member
In attendance:	Grace Norman – Deputy Director Public Health (joined at 10:30) Plus support staff

Welcome:

The Chair welcomed everyone to the Panel meeting in public, and reminded people the meeting is being recorded.

A recording of the meeting is available upon request via the publichealth@gov.je mailbox. There is a slight delay in the recording being available as appropriate checks are made to ensure anonymity of the observers attending.

The Chair recapped in the meeting that the Panel would be producing a series of five reports:

- The 1st report is the current report in progress which is an interim report on feasibility of therapeutic phlebotomy as a way of supporting people who have elevated PFAS levels in their serum and collecting evidence on that data on how much it helps or otherwise. The interim report is being done now to offer something relatively quickly before deliberations are done for the final conclusions.
- 2nd report – more detailed, on health impacts of PFAS exposure and particular groups of the population that might be at increased risk or reduced risk, as well as what parts of the body it can impact upon and potentially the levels at which those impacts happen, depending on what evidence is found.
- 3rd report – more detailed and will look at all potential treatments for people who have been exposed to PFAS, and evidence of how effective those treatments are as well as looking at other interventions and testing. Therapeutic phlebotomy will be looked at again at that point.
- 4th report – focus on the environment, how to reduce exposure, environmental interventions, how to help manage PFAS in environment.
- 5th report – update to first 4 reports, and any further information and evidence available and any changes locally.

Introductions:

The Chair and Panel members introduced themselves.

Dr Steve Hajioff, Independent Panel Chair – A background as a physician and a retired Director of Public Health from an area of London with two major international airports and a variety of other environmental challenges. Also worked for many years in designing and conducting clinical trials.

Dr Tony Fletcher, PFAS and Health Panel Member - Epidemiologist at the London School of Hygiene and Tropical Medicine, working on PFAS since 2006 and member of the panel with

experience of studies on the health effects of PFAS in West Virginia in the United States, in the Veneto region, in Italy, and in Ronneby, Sweden.

Professor Ian Cousins, PFAS and Environment Panel Member - Professor at Stockholm University, an expert on PFAS, appointed as the environmental expert on this Panel and whose expertise on PFAS is on the sources, transport, fate, and exposure of PFAS.

Grace Norman, Deputy Director of Public Health for the Government of Jersey, the Commissioner for this work, and a standing observer at these meetings.

Support staff, for programme management and administration were also in attendance.

It was explained that most of the scientific evidence available has been reviewed and the main function of today's meeting was to discuss what we understand from that evidence, and what potential inferences we can draw from it, to arrive at the conclusions.

The islanders who have been exposed to PFAS were requested to send their comments to the PFAS panel mailbox pfaspanel@gov.je at the earliest convenience so the comments and queries can be incorporated into the meeting in September, when recommendations from the interim report will be discussed.

This particular report *(report 1, interim report on feasibility of therapeutic phlebotomy)* has been a truncated process so that the Panel could potentially stand something up quickly to potentially offer help for people who might wish for it. That doesn't mean that this hasn't been a robust process, it just means that the Panel haven't had quite as many layers of consultation on this one as they are planning to have for the next reports. The processes on the other reports will be more detailed.

Declarations of interest

None to add.

Minutes and matters arising

The minutes of the last meeting from 07 July, were taken as read and agreed, with no matters arising. These cover the detail of the discussions with the subject matter experts.

The chair mentioned that it would form the kernel for one of the chapters of this report along with the other 3 documents that will be discussed today.

Additional findings since the last meeting

Since the last meeting, the panel have had some debrief conversations with the subject matter experts. The chair also met with a group of islanders yesterday and there were themes from those discussions which will be deliberated on today. These included, the historical beliefs around phlebotomy and bloodletting, and the importance of that. How evidence based the European standard HBM *(Human Biomonitoring)* levels for PFAS are and how important they are in guiding decision making. The background levels in Jersey amongst the non-exposed population and how we find out more about that. Following the last meeting, Professor Kristina Jakobson *(University of Gothenburg / subject matter expert)* highlighted the issue around PFAS in women of childbearing potential, the issue of vertical transmission to the unborn baby or potentially during breast feeding. Several experts also raised the topic of how much we can infer on the link between lowering levels of PFAS and improving health outcomes.

Also, what constitutes a laboratory, that is good enough to do testing was raised, because that will need to be a practical part of any phlebotomy program to measure whether it is working or not and the extent to which it's working.

Update on the 3 reviews: To inform the interim report on therapeutic phlebotomy (report 1)

Dr Tony Fletcher presented and talked through the draft review.

The available literature on PubMed was researched and 3 studies were identified where specifically phlebotomy had been used to try and reduce body burdens of PFAS. In addition, there were a couple of studies that were observing populations, including a questionnaire on how often they did phlebotomy, which gave an idea about whether that led to an extra reduction comparing people who had phlebotomy and people who hadn't, which pointed in the same direction (because they didn't know how long ago the phlebotomy was to estimate the amount of reduction due to phlebotomy, and so these studies not included).

The available studies were summarised very briefly which was helped by the discussions last month as the two subject matter experts invited were each co-authors the key studies and that was quite useful to flesh out some of the interpretation of what the Panel could read from the papers.

Literature review on phlebotomy

The first study which was the Genuis study, was of a small family group. Where six people in Canada had been exposed through excessive use of Scotchgard carpet treatment.

There was a use of phlebotomy to reduce this heavy body burden and because of using multiple repeated phlebotomy they had a significant fall in their body burden at the end of the year. This was compared to what it would have fallen to had they done nothing, because people all excrete it to different degrees.

In the Genuis study, the average fall was 29% over a year for the individuals participating in this phlebotomy program, but it would have fallen by 12% anyway, so the difference between those two (17%) would be the drop you get from phlebotomy activity. This can then be divided by the number of phlebotomies they had and see that on average their fall was 4.48% or 4.5% drop in their serum PFHxS due to a phlebotomy process, which is a standard 470 millilitres of blood being taken. This is the median value in this small population of 6 adults.

That calculation of the drop has been done for each of the compounds and other studies. For PFOS it went down to 47.7% and for PFOA 28.5% (taken from % fall per year in Genuis et al 2014). This calculation of comparing the drop, subtracting with what it would fall anyway, and then normalising it per phlebotomy procedure, has been done for the other studies as well.

The chair commented that this per intervention reduction is a really useful measure knowing the impact that one intervention potentially has on people, in terms of having to go somewhere for a procedure, over and above looking at a theoretical program is really important.

Professor Ian Cousins commented that the original Genuis study compared the average drop and the drop percentage fall predicted by phlebotomy to an Olsen study, which was for retired workers. Dr Fletcher had done some additional work to compare it to the Swedish population study, which we think is a better study for comparison as the study has got men and women, closer in age and they are not retired workers and include other community population.

There were some people who had concerns regarding the data set in the Olsen study, so this *(Swedish study)* was a better comparison.

The Olsen study also stands out as it has the longest half-lives of any study that's ever been published. The long half-lives in the Olsen study are understandable if you have a population that skews much older and might have reduced kidney function and other issues that might make it harder for them to eliminate toxins from the body.

It is also a very small population of around 20 (Olsen study) compared to the Swedish study which includes around 100 people.

Another complication looks like the rate of excretion, more rapid initially in the first year and then in the second year, it's somewhat slower. So, depending on how long you leave it, from the ending of the exposure to measuring the half-life, you will get a different value. The variability could also be because you're getting closer to background exposure, it is having an impact on the half-life.

The issue of variability which the Panel have mentioned before, perhaps ought to be emphasised more in the paper, is that the percentage fall per year, the 29% drop is the average and within that small family and there is already a wide variability. The expected fall again is an average and there's a big variability in the populations we study in the half-life for each individual, which on average is about five years for PFHxS, but variability is measured from under two years up to ten years when looking at individual half-lives.

Dr Fletcher commented that if he was deciding whether or not to get phlebotomy, that he almost certainly wouldn't get those average values that are expressed here, as he might be a much more rapid natural excretor or much slower, naturally excretor than the average found.

Predicting the average benefit in relation to the average fall in a population (for an individual, that may be well above or below that average) is an inherent problem in extrapolating from average population risks to an individual impact.

Professor Cousins commented that some individuals may not clear PFAS very quickly at all whereas other individuals may clear PFAS very quickly, we don't fully understand why there is a big variation as no good reasoning found in in the literature. You could guarantee that you will get a percentage fall from phlebotomy but may also have a large percentage fall from natural clearance.

Dr Fletcher then spoke about the he second study which is a more classic randomised intervention. They have taken a group of firefighters who have got moderately elevated levels that is above the general population. They have divided them into three different groups where one group has had phlebotomy, another group had plasma donation, and a third group had no interventions. We can directly see the drop in the intervention group compared to the control group. The baseline has fallen for PFHxS from 3 to 0.6 (ng/ml) to an average drop of 16%, and then given they had 4.3 phlebotomies on average each, you can divide that and get the average benefit from a phlebotomy intervention, which for PFHxS was 3.8 for PFOS was 2.3 and for PFOA was 5.8 (ng/ml). *Ng/ml = nanograms per millilitre.*

PFOA has been mentioned as approximate as the estimates of the baseline and the drop are a little imprecise, but the figures are similar to those found for the Genuis study.

In the same population they had another procedure called plasma donation, which is more complicated, however, it is not currently on offer in Jersey as it requires a complex machine to take the blood out, extract the plasma and then reinsert your own blood cells with replacement for the plasma. On calculation one gets slightly smaller estimate of the benefit than directly from phlebotomy. The predicted fall from phlebotomy from extrapolating from the plasma donation would be 1.5, 1.4, 3.7% drop per 470 millilitres of blood and the equivalent amount of plasma that was removed in the Gasiorowski study including Australian firefighters.

The chair commented that we will be considering in detail plasma donation and plasmapheresis in report 3. The reason why it is out of scope for this report is as it would take

much longer to stand up a plasma donation service than to set up a therapeutic phlebotomy service. So out of scope in this report 1.

The chair noted that it is interesting that there is a slightly lower clearance rate from an individual plasma donation than from an individual whole blood donation. Each one of those donations is a unit of inconvenience for the individual as they may have to travel to a donation centre, so it is a consideration as to how effective a use of the public's time of different interventions are. The advantage of plasma donation is that it can be done more often however, to get an equivalent or better result the individual will need to travel to the donation centre frequently.

It can be seen that the overall drop from the plasma program per year was more than the drop got from the phlebotomy which could be as it can be done more frequently, and you are not losing red blood cells, so a bigger volume of plasma is removed per year under the plasma donation system, which is of greater cost and inconvenience, although a greater amount of plasma can be removed.

The smaller fall from the equivalent amount of plasma being taken in these two procedures might be because of this frequency, because when you absorb PFAS, a lot of it is in your blood, but there's also other compartments in the body. If you remove all the PFAS from your blood and replace it with totally clear blood, it will get topped up again from the other compartments sitting in the kidney or liver which then redistribute so that it's more evenly distributed in the blood and in other organs as the secondary compartment. It may be that what we see in this study is that the plasma donation is more frequent and there's less time for the blood to be topped up again. Which could be the reason for removing less through repeated donations than from blood when you need to wait two months before the next phlebotomy when there is plenty of time for the blood to re equilibrate from the other compartments.

Another potential explanation is that a proportion of the PFAS binds to the red blood cells and therefore is removed with the red blood cells, however it is less than 10% as estimated in other papers so it would not explain the two-fold difference in this drop.

The third study is not fully reported. There is an Italian report available, produced by the region of Veneto. They reported preliminary results of a program that they started to reduce body burden for PFOA in particular. In the summary it was reported that from the start of the program, from an average serum concentration of 113 nanograms per millilitre there was a 35% drop from an average of about 6 procedures. From estimate, the potential drop per phlebotomy seems to be 3.7% reduction identical to the previous study mentioned. It has however not been reported in full, as the program was terminated from offering phlebotomy to the population, hence this is the only data available from that study, but it is consistent with the other data.

Pharmacologists have this concept of volume of distribution which is that effectively when you measure the concentration of a drug in the plasma, it's diluted not only in the plasma, but in the other compartments of the body, so the effective volume is called the volume of distribution. It has been estimated for PFAS in different papers (with some uncertainty) that this varies from 100ml/kg *(millilitre per kilogram)* up to four times that volume. If those values are applied to a 70-kilogram adult, on doing normal phlebotomy around 1% would be removed, which would be higher for someone 50kg and lower for someone 90kg, which is the largest estimate of volume of distribution. For the smallest estimate of 100ml/kg, the average drop will be about 4%. From this pharmacological approach, you could estimate that the average

benefit would be in the range of 1 to 4%, which is a little lower, but in the same ballpark figure as the ones directly from the three studies mentioned above.

Figure 4 in the draft review summarises the findings of the interventions from the 3 studies in one table and was shared on screen in the meeting.

	PFHxS		PFOS		PFOA	
Study location:	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy	Serum med. conc. ng/ml at baseline	% reduction from 1 phlebotomy
Canada (phlebotomy)	109.3		39.5		5.7	
		4.48		7.72		1.47
Australia (phlebotomy)	3.6		10.9		1.2	
		3.88		2.35		5.81
Australia (plasma)	5.2		11.7		1.1	
		1.47		1.35		3.7
Italy (phlebotomy)					114	
						3.7

Source: (Genuis, et al. 2014), (Gasiorowski, et al. 2022), (https://www.quotidianosanita.it/ 2017)

The first column for the two different studies shows the average starting blood concentration at the beginning of the intervention and what's the expected percentage reduction that you get. For the two direct phlebotomy estimates it was 4.4% and 3.8% for PFHxS and a little lower estimating from the plasma extraction. For PFOS, 7.7% and 2.3% which is rather less consistent between the two studies, but the reduction is there and for PFOA it is the other way round with 1.5% and 5.8%.

The uncertainties may be because of the real differences in how we mobilise these compounds. The fact that one is higher than the other in one study and in another direction in the other study suggests that this is a small study random variation rather than any evidence of a systematic difference between compounds or between the countries where it's being measured. A reasonable midpoint estimate of the benefit of these procedures for any of these three compounds would be around 4%, but with a wide range of uncertainty around that average benefit.

The chair queried if there is a possibility that some of these differences might relate to the different half-life decay curves of the different compounds based on the duration between the exposure and the phlebotomy intervention. Assuming PFOA had already decayed quite a lot in quantity by the time the intervention started in one particular jurisdiction, it's percentage reduction would be less in that study than in another study when it was at relatively high levels.

The Australian firefighters were still being exposed, so there was no time difference between stopping exposure and then following a decay curve.

In the Canadian study the primary exposure was reduced, but there was still household dust that was giving them a lower-level exposure throughout, and the intervention started while the primary exposure was still active. Halfway through phlebotomy, they removed all the carpets and replaced them with wooden floors, but the dust remained.

If that is the case, there wasn't much time difference between ending exposure and starting the intervention. To summarise about the variability, we know that the rate of excretion varies

with sex, with age, probably with time since first exposure and if the level of exposure is not clear. If you are close to background then the benefit is much smaller because effectively the benefit is between what is in your blood and what would be the target level if you waited, as eventually it would tail off at a certain level which would be the same as everybody else due to the levels circulating in the environment, whether household dust, food wrappings as there is an average level (of PFAS) in the population. The Panel don't know the background level in Jersey, but the background levels in other populations have been mentioned in the paper.

The European Union study summarises 20 different surveys across countries in Europe. In that study, there was quite a consistent result between studies. For PFHxS, most of the background measurements is 0.2 to 0.5 ng/ml which is much lower than any of the measures mentioned in our last 3 studies. For PFOA it is a little higher around 0.5 to 1.5 ng/ml and for PFOS little higher still at 1 to 3ng/ml.

For example, if your PFOS level was 4 *(ng/ml)*, you would have very little benefit from having phlebotomy every week because it would probably only go down 4% of the difference between your level and the background level. If the typical background was 2 *(ng/ml)*, then the reduction would only be 0.08% in the body burden from doing it. If your level was 50 ng/ml, then the difference between 4% of 50 and 4% of 49 is negligible. So, 4% of your total measurement should be expected to go down which has been illustrated in the figures in the draft paper for PFOS and the reductions.

To summarise, the average benefit will be expected to be about 4% reduction per *(phlebotomy)* procedure (surrounded by some uncertainty about the true average from other studies due to the variability and some uncertainty about where you fall within those range of response rates individually). If you had the maximum of 6 procedures allowed per year, that would be a 22% fall, but it would be substantially less than that if you were close to background and virtually no benefit at all if you were very close to background levels.

Structure of a clinical study

The chair presented the review and commented that some of the study designs outlined in the paper would not be appropriate in this situation, but it was about triangulating what we are doing and what the Panel potentially could do against some of the evidence that they are going to be looking at. The chair mentioned this could be useful for the later reviews, also understanding some of the things to look at in report two, and report three when they start drawing distinctions between what we call the strength of evidence between different studies.

There are a variety of different types of study. Attendees were invited to refer to the paper.

There are studies when there is an intervention and a measurement is made of the effect of that intervention, studies when a large group of the population are looked at to see what happens over time, studies where the population as a whole is looked at in one point in time and they all have different benefits and potential disbenefits that are that that are discussed in the paper.

Key points in selection of study modality are the ethical considerations. The need to go through an ethical approval process is really important but can create a delay. Therefore, the delay needs to be borne in mind when choosing the study design where the rationale is to do something practical with some pragmatic data collection.

The second point is the cost of delivery, as there can be implications for different choices without pre-judgement. Cohort studies, for example, are very expensive to deliver, and even randomised controlled trials of the sort that were undertaken in Australia can be extraordinarily expensive. The chair noted he had been involved in trials that cost a $100 million to deliver. If

the Panel were to recommend a randomised control trial, there is a question about proportionality.

Finally, is the study size requirement in order to ensure meaningful findings and do a control group comparison, you need people in that control group who have also been exposed and are not receiving the treatment in question, which is problematic when you have got a relatively small group of people who are known to be exposed and to have a risk associated with that exposure. So, all those things will play together in deciding how to deliver any sort of study. We can come back later and talk about which study types might be preferable in this situation.

The chair commented that the other piece is on literature-based studies, which is the systematic review and the meta-analysis and thought it was important to clarify something around the methodology as when we review the scientific literature, in effect there will be a structured approach which is somewhat different from, reading a paper and taking the conclusions of that paper and then adding it to what you have seen elsewhere. We might end up with different inferences being drawn across the whole body of the literature, than might at first be apparent to some, because there is a very specific methodological approach.

Dr Fletcher commented that if there is a relatively small group for an intervention to reduce their body burden, based on the data summarised we would know the benefit from an intervention however we would not know how much reduction you might get and one could measure this either through a monitored intervention where you measure before and after and compare it to the general expectation, as with the Genuis summary. Or you could subdivide them into two random groups giving intervention to one group and withhold intervention from the other group.

If the objective is to reduce the body burden in the population and to assess how much it is being reduced, this could be an intervention with monitoring rather than a randomised or case control study.

The chair commented that there are more reasons why something like a randomised controlled trial might be problematic. For example, people within the control group might not like the fact that they have been randomised to the control group and might go and donate blood, and they might not inform that they have done so which will make the results uninterpretable. Also, the numbers to have an intervention, a control group are very small and in a randomised controlled trial, we would need to go through a formal ethics approval process which would mean we cannot get any offer up and running until then.

Dr Fletcher queried that if it's just an intervention with monitoring, does that require the same level of ethical approval? The chair replied, not particularly where there's been something that might generally be available anyway. There will be a piece probably around ensuring appropriate confidentiality and consent for which it would be wise to get ethics committees view on but not necessary for a service evaluation or a case series, which is where the panel might end up. The chair commented that he was deliberately completist here *(in the review),* partly because it's better to do more and then then take some out and partly because possibly the Panel are going to want some other things on study design in report 2 and potentially report 3 and 4 as well as part of the discussions. The content is now available to reuse later.

Those who are observing (members of the public) were encouraged to comment through the PFAS mailbox on any of these papers and discussion from today.

Dr Fletcher commented that they have endeavoured to identify all relevant studies for looking at the impact of phlebotomy on PFAS levels and was fairly confident that anything that is

published would have come up in the various searches done. Although, there is grey literature of things that get published a little less formally, like the example of the Italian study, which never got into the peer reviewed literature. If anybody from their own searches here have identified other things that would be useful to include in that review, then please let the Panel know.

The Panel are going to include some other studies, for example the studies on menstruation where women have lower concentrations than men because of regular blood loss, which is relevant because this is very much work in progress. It is not a polished final version that the Panel are sharing these reports in the middle of the process, but they are in good shape.

The chair explained that the reason why they are watermarked ‘draft’ is because that's exactly what they are and that is one of the reasons why the Panel are inviting comment and questions so that they can continue to improve what they are doing going into the final report.

Once again, the public was requested to please bear in mind that this particular report is an interim one on a very specific intervention, and the Panel will be going into much more detail on the health impact and subgroups of the population in report 2 and on all interventions in report three.

Review of risks to individuals to giving blood

The chair presented review 3, which is a very brief analysis on what the literature says about risks and benefits of phlebotomy. There was no specific literature that the chair could find through a traditional literature search on specific risks of phlebotomy for therapeutic purposes. There are a few conditions where blood is taken, to improve the health of the person it is taken from, these are disturbances of the blood itself or certain chemicals building up in the blood, with iron is a particular example.

There is an extensive literature on blood being taken for donation purposes. The first assumption here was that the effects of taking blood for a blood donation will not be vastly different from the effects of taking blood for the purposes of PFAS body burden reduction. It would have been difficult to produce anything without that assumption, but nevertheless it is an assumption that's been made in this work. Generally speaking, most of the restrictions around blood donation are in order to protect the recipient of the blood rather than to protect the donor, and again, that needed to be unpicked, but it also does suggest that the risks to the donor are extremely low.

There are local reactions at the site of taking the blood, whether it is an infection at that site or whether it is excessive bruising, or whether it's some bleeding afterwards, which are very likely to be self-limiting and not produce a long-term impact, but to be aware of.

There are issues around the depletion of the red blood cells, the person's haemoglobin, which is the thing that transmits or a moves oxygen in the blood, goes below a certain point because it was already quite low and that will be what we would call the risk of anaemia. Highlighting that as a potential risk, which would then potentially inform what the Panel might set for thresholds for an intervention down the road, as would not want an intervention to risk doing harm to people.

The third, which is similar to anaemia, is the reduction in iron in the body, which is itself a driver of anaemia. The Panel might want to take a view on the iron level in the body at which it is safe to take blood. Because your blood volume reduces from donating a unit, it can potentially drop your blood pressure and that in turn can potentially cause light-headedness and fainting. Looking at potentially whether there are blood pressure levels below which the risk gets higher. The chair expanded to say that there is also a risk of fainting and dropping of

blood pressure, not because of the blood volume being reduced, but because of an anxiety response to the procedure that does affect a small number of people, more males than females. So that needs to be considered, because if someone either has needle or phobia, or does become lightheaded in response to a blood taking in general, then that potentially is an issue.

The chair commented that he didn't think it would be appropriate for the Panel to look only at potential risks, without looking at benefits. They did review the literature on potential benefits as well, however, said that these really do need to be taken with more than a pinch of salt because the evidence for the benefits is relatively weak and there is significant likelihood of what those trained in epidemiology would call confounding.

There are two areas where there does appear to be benefits over and above phlebotomy being used to treat a disease. The first is around heart disease. The evidence there is very weak and there is potentially significant confounding around this one. Additionally, there is some literature on the act of altruism improving health, so that could be a driver. There's also the potential of how affluent the individual is, might have an impact on their heart disease state and what we don't know is whether the people who donate blood altruistically are representative of the overall population or not. Certainly, a proportion are excluded because people have other illnesses that would render them unsuitable to be blood donors from the recipient's point of view and those people are often at more risk of disease. It could be that is an apparent association without strong meaning, the Panel can't really draw too many inferences.

There is a similar piece where the evidence is slightly stronger, but still very weak around cancers, and the same caveats about confounding apply there. The additional one is whether they are matched, because the risk of cancer increases with age, and if you're blood donor population are somewhat younger than the overall population structure, then that could also explain that finding.

Those are the things the chair thought was important to pull out because those are some of the decisions the Panel would need to make if they were to suggest a phlebotomy intervention.

The big picture is that for a specific people who have anaemia or too much blood cells that might benefit from phlebotomy the general health impact could be positive or negative, however cannot say.

The chair continued saying that the negative is very small, and the potential positive is tiny and unproven. Where it would land overall is other than in those specific groups where there is increased risk. The chair did not think that there is anything there that would suggest phlebotomy is not a good intervention and (with a very strong following wind) there may be some additional benefits as well.

If a phlebotomy program was offered, it would be reasonable to have a threshold around blood pressure, haemoglobin level and total iron level for someone known to be anaemic.

When giving blood as a blood donor, a lot of places set thresholds around those sorts of thing as well as body weight thresholds and some have age thresholds, upper and lower.

The chair commented that the first question is, do we need to do something different than blood donation services in terms of where they set thresholds, and then the second one is, should we be setting thresholds around those things? The third one is, given that this is theoretically an intervention with potential benefit for the person rather than an altruistic act to benefit another person, do we look at being a bit more relaxed about some of those thresholds in order to offer the potential benefit of intervention more widely?

Dr Fletcher queried if we know how strict the thresholds are at the moment? If I go to a blood donor centre in Jersey, do they test my blood pressure, do they do a haematocrit first?

The Panel were unsure of the answer at this point and will need to drill down into it to make recommendations. The Panel are aware of an upper age cut off at 65 *(for general blood donation services)*. It may be that they would take that a view that if someone was slightly older than that, but extremely fit and healthy otherwise, but had an elevated PFAS level that the balance of benefit and risk would be different than them being an altruistic donor. These are issues for the Panel to explore.

The Panel have not yet looked systematically at the potential risks of PFAS, but the likely conclusion is it is impossible to quantify the benefit in health terms of, the percentage reduction in the chance of developing cancer or hypercholesterolemia or other issues. Dr Fletcher commented on what would be the quantifiable benefit in terms of percentage reduction in risk is unlikely to be possible, so the benefit is in terms of reducing your body burden in case there's a risk, but not quantifiably.

The chair commented that to counter that is the feeling that one has been exposed to a risk, even if the physiological impacts of that are relatively small, does not mean that there won't be psychological impacts over that and being able to offer reassurance or support in one way or another may help with those equally as much as it might help with physiological issues.

Professor Cousins commented from his own individual perspective knowing that there's a relationship between exposure and risk that reducing the levels in your blood or exposure is going to make you feel more confident that you are less likely to have an effect even if you cannot prove it at the individual level.

Dr Fletcher commented that it depends on the extent to which it is above background levels and it's hard to put a number on that. One can take extreme examples and say if it's above 30 ng/ml for any of these three PFAS compounds, then there's clearly an overwhelming benefit even if you're over 65, you might want to be offering that. But if your level is only 2 or 3 ng/ml close to the background level then he wouldn't encourage them to give blood, but in the middle range between 5 and 10 *(ng/ml)* it is tricky.

Professor Cousins said it is not going to reduce your exposure because of background exposure so it's going to be topped up all the time is the issue. It will reduce it to some extent, but not much.

The chair mentioned that Professor Kristina Jakobson, *(University of Gothenburg subject matter expert)* also alluded in discussions after the last meeting that it would be very difficult to have a phlebotomy programme or any other treatment programme without knowing what the background serum levels are in the unaffected population in Jersey. They could assume on basis of European average but that might not be as robust. Professor Jakobson made suggestions that that if we do go down this road, we do find a way of testing, possibly through prior blood donations anonymously from elsewhere on the Island, testing what background levels are.

The only caveat to that is there is currently a considerable lead time to getting the results of testing because of the laboratories used to date in the United States has a transit time and backlogs. It would be problematic to delay starting any program if we go down that road waiting for those results. The Panel might want to take a view that background level testing was done, and a program was stood up pending that result, which would probably give the exit criteria for an individual. Once the level reaches background or approaches background level as Dr

Fletcher had shown in the paper, phlebotomy gets less and less effective which would give us the criteria for stopping.

Dr Fletcher suggested getting a random sample of blood from donors who live on the east end of the Island, away from the airport, you can treat that as a good example of background levels. There is unlikely to be much different from the background levels that we've found in other populations, they might be one or two units higher. One could start from the assumption that it's probably going to be around the 0.51 and 2 average range identified from the European survey. Conditional on that you could make a recommendation about what level above that would justify having an intervention and then refine that in the light of more accurate data from a sample of individuals, adjusted up or down appropriately.

The chair commented on something that struck him from Professor Jakobson's presentation was that association between serum levels and potential complications, was the fact that it was a stepped graph that it wasn't a dose response all the way up, it increased up to a point and then levelled off quite a bit. On the basis of that it seems to make sense that the sort of threshold level for intervention would be lower than it might be if you had a linear response because of a relatively low level of exposure that seems to be associated with risk and then it doesn't get that much greater as the levels go up.

The second was around the HBM levels, the European safe and possibly not safe different thresholds. The question was about how meaningful they are, are they based on toxicological evidence or a best guess and how much influence should they have on setting a threshold for a phlebotomy intervention?

Professor Cousins said that it is difficult for the Panel to make recommendations based on health effects when that report is coming later. They have to go into all the individual health effects and look at those responses. He did not want to make any general conclusions regarding health effects and dose response, and they haven't started looking at that in detail and didn't think the Panel can make any recommendations in this report regarding health effects and what the intervention should be.

Dr Fletcher said as a pragmatic solution, one can borrow existing recommended limits. For HBM there is a German regulator who came up with the HBM, one and two, which were 2 ng/ml and 20 ng/ml as having nothing to worry about in that range in the middle, but it is uncertain what the levels of risks are. The second source is a conclusion tolerable weekly intake of PFAS in food stated in the report.

Professor Cousins debated if it would be the wrong way around to start taking these reports with different criteria without reviewing them first in detail which we're going to do later. The Panel have to really look at those and see whether there is a toxicological basis for setting these different criteria before we can recommend using them.

That was the basis of asking the question about the HBM, whether it was actually based on toxicological evidence or whether it was a consensus. To which Dr Fletcher replied that it is based on toxicological evidence.

Dr Fletcher then commented on research on human and animal data and body burden in mothers and immunity around childhood vaccinations. *To note there was some interruption in the signal at this point.*

The chair commented that the consensus seems to be that they might struggle if they were to set a threshold and inclusion threshold level that was widely higher than HBM or the other standards. There doesn't seem to be a strong reason that's come up in the discussions at this

point why we would feel the needs to override those. Even with the caveat that the Panel are not 100% certain that those standards are as robust as they need to be for a substantive approach.

Professor Cousins said they would have difficulty coming up with completely different recommendations than that are already in the literature.

The chair mentioned that they haven't picked up another point that both Professor Kristina Jakobson, *(University of Gothenburg)* and Dr Roger Klein (*PFAS Expert, Chemist and Medic -subject matter experts*) made in the discussions after *(the last meeting)* around the priority around women of reproductive age, pregnancy and breastfeeding. Noting that it is unusual to donate blood in pregnancy. Potentially we have a priority group of women of reproductive age.

Another point is that most authorities have a minimum body weight limit for blood donation around 50 kilograms however there may be individuals from the priority cohort who have lower body weights. One suggestion that Roger Klein made was, could the extent of the phlebotomy (how much blood taken) be varied in people of lower body weight? It was queried if that would be a feasible thing to manage offering something so that priority cohort can access, or would we need to be stricter around the body weight thresholds?

There are potential risks and benefits of making either choice and it maybe is something that would need to be thought on further and as the Panel work on the discussion in the paper. It's probably something we do need to consider maximizing the potential opportunity from any program the Panel recommend.

Dr Fletcher commented around the body burden and levels for women of childbearing age. *To note there was some interruption in the signal at this point.*

In addition, the number of phlebotomies women have needs to be discussed.

The chair commented that the Panel don't have a clear answer on this. Following the last meeting Professor Jon Martin, *(Stockholm University, subject matter expert)* suggested to do phlebotomy for four years, though the Panel are not convinced that's necessarily the case as he was dealing with much higher levels in the Genuis study population than we may be looking at. So, the duration of the intervention doesn't necessarily need to be as long.

As per Dr Fletcher's analysis you could potentially construct a curve on the basis of number of interventions, plus background reduction and then triangulate between that the inclusion criteria and your background level and recommend the number of interventions on that basis.

To clarify, maybe not specify a number of interventions now, but actually model the data and see that it might be different for different people depending on what they're starting level is and where the background level is in the population.

Dr Fletcher suggested possibly doing a pilot.

The chair said that the whole program the phlebotomy, if the Panel go down this road, is a pilot in effect so there is the scope to adjust during the program on the basis of emerging findings and one of the things that the Panel already talked about is that they would want to collect data.

The Panel want to have additional blood testing on people who are going through the program so we can know things about their health and maybe have them reporting symptoms as well as they were to go through a program if were to go down that that road. That could also feed back into any review of duration of treatment.

The final piece is that any pilot program would almost certainly still be running as the Panel get to the publications of reports two and three. It may be that depending on what the Panel find in doing report three that there's a sort of hand off from a pilot into something different.

The next meeting is on 6th of September, when the primary discussion will be around recommendations. The Panel may then tease out some of these issues in a bit more detail at the beginning of that meeting as a lead-in to producing draft recommendations within that next meeting.

Any other business (AOB)

None discussed.

Date and time of next meeting:

6 September, 10:00am (online)

The chair thanked all that attended the meeting and apologised for over running on time. The meeting was then closed.