First Report of the Independent PFAS Scientific Advisory Panel for Jersey – The potential for an interim therapeutic phlebotomy service (DRAFT).

October 2023

Executive summary

In response to concerns raised about historical exposure to per- and polyfluorinated alkyl substances (PFAS) as a result of certain firefighting foams at Jersey airport finding their way into private water supplies, the States of Jersey, through the public health team, undertook a programme of blood testing in the plume area. People with significant exposure and clinical findings consistent with PFAS exposure were tested and many were found to have serum PFAS levels above that considered background in the academic literature. In response the States of Jersey commissioned an Independent Scientific Panel on PFAS to gather and review evidence and to make recommendations back to government of the size and nature of any risks and any appropriate mitigation interventions. This is their first report. A series of literature reviews found evidence to suggest that therapeutic phlebotomy; taking blood in order to derive benefit for the donor; might help reduce the amount of PFAS in people's bodies without great additional risk; and may also help increase knowledge on the subject. Presentations from and discussions with additional external experts came to a similar conclusion.

In the wake of those discussions and further debate within the Panel in public meetings, it was resolved to make a series of recommendations to the States of Jersey.

The recommendations are:

1. The Panel recommends that the States of Jersey offer a programme of therapeutic phlebotomy for residents affected by PFAS as an interim measure pending detailed review of the health effects of PFAS and the effectiveness of different types of potential interventions.
2. That therapeutic phlebotomy be offered to those people who would like to take it up, were tested as a part of the public health programme in July 2022 and who were found to have a total across 8 measured PFAS compounds of at least 10 nanograms per millilitre of blood serum. Those eligible should receive information explaining the expected impact of phlebotomy so they can make an informed choice about participation in the service.
3. That background levels of PFAS in the wider community be estimated by the analysis of altruistic blood donation samples, excess serum collected to perform other tests, or by other means. This should be done on an anonymous basis.
4. That when an individual's serum PFAS levels reach the median background levels, further phlebotomy should not be performed.
5. That phlebotomy be offered to eligible people between 18 and 65 who weigh at least 50 kg. If an eligible person is not between 18 and 65 years of age or weighs less than 50 kg, clinical judgement should be applied as to whether it is appropriate for them to have phlebotomy.
6. That if an otherwise eligible person is pregnant at any point during the programme, they are not offered phlebotomy.
7. That if an eligible person has abnormal test results such as blood count or body iron or has concurrent illness, whether they are fit to participate in the phlebotomy programmes should be a matter of clinical judgement.
8. That, by default, phlebotomy should be offered every 2 months with a maximum volume of 480 ml withdrawn no more than 6 times in a year, but intervals could be increased or blood draw volumes reduced on the basis of clinical judgement about a specific individual.
9. That there should be ongoing testing before, during and after the programme to include:
    a. PFAS levels, including the 8 specific PFAS compounds detected in the first measurements in at least some individuals – PFHxS PFOS PFOA PFHpS PFNA PFPeS PFDA MeFOSAA
    b. Full blood count
    c. Iron studies
    d. Cholesterol
    e. A rating of the severity of any symptoms that were present prior to the programme
    f. EQ5D-5L or similar tool as a measure of overall quality of life
    g. A record of any adverse effects experienced during the programme

10. That a clinical history, including any activities that may have lowered PFAS levels (such as blood donation, taking medications like cholestyramine or probenecid and reproductive history) be taken from every participant.

In Report 3, on the treatment and testing of people exposed to PFAS, recommendations will be made as to whether anyone not included in the previous testing programme should be tested and what treatments might be appropriate if they have elevated levels.

Non-technical summary

Fire-fighting foam used at Jersey airport contained chemicals called PFAS, and these had polluted some private water supplies nearby, leading to concerns among local residents. Because of this, the Public Health team, who work for the Government, arranged to do blood tests in people who had drunk water from those private supplies and had felt unwell in ways that they thought might be related to the PFAS. These tests confirmed that some people had higher levels of PFAS in their blood than might be expected. After this, the government set up the PFAS Scientific Advisory Panel, of three independent scientists to give independent advice. The Panel will look at what PFAS chemicals can do to people's health, the best ways to help get the PFAS out of people's bodies and the best ways to help get the PFAS chemicals out of the water and environment.

The first of a series of reports is about "phlebotomy", which is where a pint of blood is taken from someone like when someone gives blood. The Panel considered if this could be an effective way of reducing the amount of PFAS in the body for people with high levels. Once exposure has stopped and people are drinking clean water, the amount PFAS in people's blood goes down, but only rather slowly. The Panel reviewed the published scientific reports to see if there is evidence that phlebotomy would speed up the removal of PFAS. The Panel also heard evidence from three subject matter experts who have experience in using phlebotomy for PFAS. The Panel concluded from their work that taking blood would be expected to lead to a small reduction in the concentration measured in the blood, about 4% per blood draw. This this can be done once every 2 months, giving about a 22% fall after 6 times in a year. This is faster than the natural rate of reduction.

The Panel, after reviewing the evidence and following a lot of discussions in public meetings including with experts from around the world, made 10 specific recommendations set out in the report. They recommended that phlebotomy should be made available to people who have had their blood tested already by the Government and where they have more than 10 nanograms overall of 8 different types of PFAS per millilitre of serum in their blood. Some people will be advised not to give blood, for example while pregnant, and a doctor will advise if there are any other medical reasons such as low iron. Regular blood tests will check that if the blood draws are working, so people can stop when they get down to normal levels. Checks will be done to make sure that there no unwanted side effects and to see if taking the blood is helping with things like cholesterol levels.

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Background

Per- and polyfluoroalkyl substances (PFAS) comprise a group of over 12,000 synthetic chemicals used in a wide range of consumer product and industrial applications around the world since the 1940s, including, from the 1960s, in fire-fighting foams, the manufacture of non-stick cookware, water repellents, and food packaging (Glüge, et al. 2020). Their chemical stability and resistance to degradation (Cousins, et al. 2020) has led to long-term environmental contamination and the toxicological profiles of certain PFAS (Agency for Toxic Substances and Disease Registry 2021) have led to concerns regarding possible human health effects (Buck, et al. 2011).

The main source of concern in Jersey relates to the historical use of PFAS-containing aqueous film-forming foams (AFFF) used in firefighting. PFAS-containing AFFFs have been effective in extinguishing liquid fuel fires but have long been identified as a significant source of environmental contamination (Prevedouros, et al. 2006). These foams were in use at Jersey Airport and its on-site training facility in the parish of Saint Peter. Groundwater near the airport and, as a consequence, some private water supplies became exposed to PFAS. In 2006, mains water was extended to the area, and therefore the exposure from the airport is believed to have ceased. While AFFF use and consequent exposure started some years ago; before potential environmental and human health risks from PFAS had come to light; the persistence of PFAS in the environment and in the human body mean that there are still concerns today.

In response to the concerns that had been raised, a company called Arcadis were commissioned in 2018 to survey private water supplies for the presence of certain PFAS, and an Officer Technical Group (drawing its membership from environmental health, public health, consumer protection, Jersey water and others) was established by the Government in 2019 (States of Jersey 2023).

In 2022, an initial programme of blood testing was arranged for people who had regularly used borehole water supplies in the affected area as a source of drinking water and had symptoms consistent with conditions that have been associated with PFAS exposure.

In 2023, the Government of Jersey made provision, through the public health team, to commission an independent group of scientists to assess the current situation in Jersey, with regard to PFAS, and make recommendation for actions to be taken. The Independent PFAS Scientific Advisory Panel has three standing members and a standing observer from the public health team. They have regular, publicly livestreamed, meetings where they hear from subject matter experts from around the world, as well as from affected people in Jersey (experts by experience) and explore the key issues brought to light as well as those from the scientific literature. In this review, no experts by experience expressed an interest in giving evidence to the Panel meetings directly, but email contributions were requested throughout the process and there were regular meetings face to face with nominated representatives of affected persons. The standing Panel members are:

- PFAS Scientific Advisory Panel Chair, Dr Steve Hajioff

  Steve Hajioff is an experienced leader with over 30 years as a practicing doctor in the health sector and more than two decades in leadership roles and public health practice: including being Director of Public Health in the London Borough of Hillingdon - an area with two international airports and other environmental challenges. He has worked for a variety of organisations including the WHO, World Bank, EU, international governments, UK government departments, the Greater London Authority (where he co-led the health impact assessment of the nine mayoral strategies), several NHS bodies, and has advised BMJ, Elsevier, British Standards Institute, Reuters and many others. He is experienced at chairing scientific panels, having chaired two high-profile guideline development groups for NICE, and also at chairing groups with a high level of political and media engagement; he chaired the Representative Body of the British Medical Association for several years and several scientific fora, regional, national and international. Steve has also served in Chief Medical Officer roles for a variety of biotechnology businesses and has been involved in many clinical trials.

- PFAS and health expert, Dr Tony Fletcher

  Tony Fletcher PhD is an environmental epidemiologist with over 40 years' work in occupational and environmental epidemiology and risk assessment, with experience of studies of exposure, biomonitoring and health impacts such as cancer, respiratory disease and metabolic disorders. He has been researching the health effects of PFAS – Perfluorinated Substances – since 2005, as a member of the C8 Science Panel which led a major investigation on potential health effects of PFOA polluted drinking water in West Virginia and Ohio. More recently he has been working in epidemiology programmes in PFAS-contaminated communities in Ronneby, Sweden and Veneto, Italy. He is currently Associate Professor at the London School of Hygiene and Tropical Medicine, where he has been since 1992, and has held jobs in the past at Public Health England, UKHSA, the International Agency for Research on Cancer (IARC) in Lyon, France, Birmingham University, the MRC Environmental Epidemiology Unit, Southampton and Aston University. He was Adjunct Research Professor in Environmental Health in the School of Public Health, Boston University, Massachusetts, and President of International Society for Environmental Epidemiology.

- PFAS and environment expert, Professor Ian Cousins

  Professor Ian Cousins is Professor of Environmental Organic Chemistry at the Department of Environmental Science at Stockholm University. Professor Cousins leads a research group focusing on understanding the sources, transport, fate and exposure of organic contaminants and is particularly well known for his research on PFAS. Professor Cousins has extensive PFAS research experience, dating back over 20 years to 1999. Some notable career highlights include being a keynote speaker at international PFAS workshops on multiple occasions and receiving several best paper awards for his research. In recent years, Ian has coordinated a large European multidisciplinary project, PERFORCE3, which focuses on PFAS. He was also chair of the recent international conference, FLUOROS 2023, where the world's leading experts on PFAS gathered. Ian's research currently focuses on better understanding uses of PFAS and investigating suitable alternatives, using analytical approaches to measure PFAS in consumer products and environmental samples, and investigating the transport of fate of PFAS in the environment.

- Standing observer and Deputy Director of Public Health, Grace Norman
  Grace Norman is the Deputy Director of Public Health for Jersey. She began working in Jersey in 2021, and took on the role of Deputy Director in 2022. In the latter role, she has responsibility for health protection, which is the branch of public health which deals with infectious disease and environmental hazards, including PFAS. Grace led the work to arrange PFAS blood testing in 2022 and commissioning the Scientific Advisory Panel. Grace is a standing observer so that she can contribute to the discussion, bringing the island perspective and knowledge from the work already undertaken.

The Panel will be producing five reports over the course of its work programme to provide best available evidence and evidence-based recommendations to the Government of Jersey, other key stakeholders like health services and Jersey Water and to wider society across Jersey and, potentially, beyond.

The five reports are:

1. An interim report on the appropriateness and feasibility of the use of therapeutic phlebotomy to lower PFAS body burden in affected individuals in Jersey.
2. A report on the current state of knowledge about the health effects of PFAS on people and an evaluation of which groups of people may be at increased risk.
3. A review of the range of interventions which may reduce PFAS body burden in those with elevated PFAS levels and the expected impacts, along with recommendations on the nature and extent of serum PFAS testing in both the affected community and the wider population of Jersey.
4. A systematic review of the technologies and methods that may be used to manage PFAS in the environment, along with key strategies for environmental monitoring.
5. An update report taking into account new and emerging evidence from the previous report areas, as well as progress made and any emergent results in the environment or population of Jersey.

All the reports will take due account of the balancing of risks and benefits and also of opportunity cost, including any potential consequences of impacts on services, and will pay particular attention to ensuring that people at greater risk are given additional consideration. The overall approach the Panel will take is:

- Being led by evidence
- Working through consensus
- Involving input from experts by experience and subject matter experts
- Public involvement throughout the process
- Default to meetings being in public
- Ability to work in private where there is a need for confidentiality
- Regular engagement with key stakeholders in addition to Panel meetings
- No surprises

Each report will follow a similar process, with an initial draft scope being agreed within the Panel and consulted on with stakeholders (including Islanders) before a final scope is developed. There will then be a series of systematic reviews of the available, relevant scientific literature and the consideration of evidence from subject matter experts and experts by experience. These draft reviews and meeting summaries will be shared in advance of the publicly accessible Panel meetings, where they will be discussed and draft inferences and recommendations arrived at. A draft report

will be prepared, integrating the various workstreams and will be shared with Government of Jersey through public health (the commissioners of the process) and with the public for consultation and comment. The consultation findings will be reviewed by the Panel and, where appropriate, the report revised. The final report will be shared with the Government to consider the findings, and launched through one or more public meetings. The Panel meets normally once a month online and the public can observe and email in comments, the agenda and minutes of the meetings are publicly available on the Jesey Government website:
https://www.gov.je/Environment/ProtectingEnvironment/Water/pages/pfas.aspx#anchor-7

In order to optimise the use of time, there may be some time overlap between consecutive reports, with reports processes starting before the previous report has been finalised.

Introduction

This report is an interim report on the potential for the use of therapeutic phlebotomy to help manage body burden of PFAS among Islanders who had their blood tested in the government-provided testing in the summer of 2022. It is different from the other reports in the series and has gone through a slightly abridged process in its production.

Part of the rationale for doing this in this order is to explore whether it is possible to offer something to help manage body burden of PFAS in the short term and to gather further data. This is pending the more thorough review process on health impacts and the detailed evaluation of all potential therapeutic approaches. This plan was established prior to the Panel taking office, but the Panel members were comfortable with the approach. The rationale for considering phlebotomy for this assessment is that a potential service can get up and running more quickly than most of the other potential interventions, it is an intervention which most individuals could access currently anyway by choosing to donate blood, and it has a well-known safety profile.

For these reasons, the Panel thought it reasonable to consider the literature on the efficacy and safety of therapeutic phlebotomy and to explore whether an interim offer to affected individuals was supported by the evidence. This is so that a service could be considered while the detailed deliberations on PFAS and health and on the efficacy of human treatments for managing PFAS burden take place, and any subsequent decisions about ongoing services are made, given that these are expected to have long lead-in times.

This report will consider the published evidence on the use of phlebotomy to reduce PFAS levels in the body and the evidence on the clinical risks, and potential harms and benefits from giving blood in general. The Panel has also consulted with other international experts on phlebotomy in regard to PFAS exposure. The Panel has looked at several models for clinical studies or information collection so that there is potential to assess further any impacts from an intervention.

On the basis of these analyses, the Panel will make recommendations to the Government of Jersey as to whether phlebotomy should be made available and what form such a service might take.

Review and analysis of the published literature on phlebotomy to manage PFAS exposure

Introduction

Phlebotomy is the donation of whole blood, usually roughly 480 ml per session. A search of the published literature on the effects of phlebotomy on the body burden of per- and polyfluoroalkyl substances (PFAS) in serum found three intervention studies, one of which only looked at a related procedure, and some observational studies. There were no studies assessing the direct impacts of therapeutic phlebotomy on health in populations exposed to PFAS.

Findings from the literature

In addition to the intervention studies discussed below, a study by Lorber et al. showed that male venesection patients, treated to relieve symptoms of disorders such as haemochromatosis, had PFAS serum concentrations 40–50% less than males of the general public (Lorber, et al. 2015). The Lorber et al. study provides further evidence that regular venesection (another term for phlebotomy) can reduce the body burden of PFAS. However, the Lorber et al. study is not comparable to the three intervention studies, nor could the effective reduction per procedure be estimated in the Lorber et al study.

In studies of PFAS where participants have been asked if they have been blood donors, associations have been noted where more frequent blood donors have lower serum levels than non-donors (Averina, et al. 2020), (Řiháčková, et al. 2023). However, while those studies provide further support that phlebotomy can reduce the body burden of PFAS, they do not provide enough detail on how often and how long ago they gave blood, and thus cannot be used to estimate the percentage reduction attributable to each donation.

There is also evidence of differences in PFAS body burden observed between males and females from the approximate ages of 13–50 years, with little gender differences outside this range. Women in studied populations who had been exposed to PFAS, had a significantly lower PFAS body burden than men. Given this age dependence, it has been suggested that menstruation is an additional route of elimination available to reproductively mature females who regularly lose around 60 mL of whole blood on average (for a 71 kg women) per month (Wong, et al. 2014). The gender differences between PFAS body burdens between men and women due to menstrual blood losses are further supporting evidence for the potential effectiveness of phlebotomy. In the summaries below, we have reported the findings from the two published phlebotomy intervention studies and summarised them in terms of the percentage reduction to be expected per phlebotomy procedure.

Genuis et al. in 2014 (Genuis, et al. 2014) reported on a family who had accumulated high levels of perfluorohexane sulfonate (PFHxS), perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in particular from repeated and large-scale use of PFAS-containing carpet treatments in their home. PFHxS was especially high, and PFOA only moderately higher than the general background population. The levels differed between different family members. Once they realised they had been exposed to PFAS and had high serum levels, they ceased using the treatments and discarded most of their carpets, replacing them with wooden flooring. Thus, the prior elevated exposure largely stopped. Although some measurements of household dust revealed some measurable level of PFAS, the exposure after the renovations was relatively low compared to their past exposure.

In the paper, an estimate of the elimination half-lives for the family were provided. These half-lives averaged about 2.1, 1.2 and 2.1 years for PFHxS, PFOS and PFOA respectively, indicating more rapid elimination than found in other studies. From their multiple phlebotomy donations, the average

amount of blood given was 1802 ml/year in this family. They compared these results to a population who had had occupational exposure to PFAS and were retired at the time of study, whose PFAS levels were monitored over time to assess natural elimination. However, a more comparable population, particularly because of age and gender mix and type of exposure, is a Swedish population which were followed up with multiple testing after ending exposure to drinking water contaminated with high PFOS and PFHxS from firefighting foam (Li, et al. 2018). In the Swedish population, reported half-lives were 5.3, 3.4 and 2.7 years, for PFHxS, PFOS and PFOA respectively. For ease of comparison, these half-lives (both for the study group and the comparison population) have been converted into the average percentage reduction of PFAS per year. The difference between the reduction in the Genuis study and the reduction expected due to average natural elimination, can be considered the percentage drop due to the intervention (average blood donation 1802 ml/year). This can be converted to the expected benefit percentage reduction for one phlebotomy donation of 470 ml. This information is summarised in

Figure 1, below.

Figure 1 Percentage reduction in PFAS, Canadian family.

	PFHxS	PFOS	PFOA
Baseline serum concentration (ng/ml)	109.3	39.5	5.7
Average % fall per year in study population	29.4	47.7	28.5
Expected % fall per year in comparison population *	12.2	18.1	22.9
% fall in study minus expected: attributed to phlebotomy interventions	17.2	29.6	5.6
% fall predicted for one phlebotomy	4.5	7.7	1.5

*Source: (Genuis, et al. 2014), * (Li, et al. 2018)*

In an Australian study of firefighters (Gasiorowski, et al. 2022) with occupational exposure to PFAS-containing firefighting foams, participants were randomised into three groups (one offered up to 5 phlebotomy interventions, one plasma donation (where only blood plasma and not blood cells are taken), and a control group (just observed with no intervention). To assess the impact of the interventions, the impact of the phlebotomy was estimated from the difference between those giving blood and those in the control group who received no intervention. On average, the phlebotomy participants gave 4.3 blood donations over a 12-month period, so the impact per blood draw can be estimated directly. (Please note, the results for PFOA are a little more approximate as they are presented in less detail in the data tables and had to be read from the graph in the paper.) The baseline concentrations, and absolute and relative reductions from phlebotomy are summarised in Figure 2, below.

Figure 2 Reduction in serum PFAS, Australian firefighters.

	PFHxS	PFOS	PFOA (approx.)
Baseline serum concentration (ng/ml)	3.6	10.9	1.2
Drop attributed to intervention (ng/ml)	0.6	1.1	0.3
% fall attributed to phlebotomy interventions	16.67	10.09	25.00
% fall predicted from one phlebotomy	3.88	2.35	5.81

Source: (Gasiorowski, et al. 2022)

One of the intervention arms in the Gasiorowski study was plasma donation. While this intervention is outside the scope of this review and will be considered in detail as part of our third report, the results can be used to estimate what might have been the reduction from phlebotomy as most of the PFAS resides in the plasma.

In the plasma donation group in the Gasiorowski 2022 study (Gasiorowski, et al. 2022) participants received an average of 6.4 plasma donations; each one "up to 800 ml". For these calculations we assume that the plasma is 55% of the blood volume and each donation was 800 ml, thus the total average donation was 800*6.3 ml of plasma, equivalent to 800*6.3/0.55 = 9163 ml of whole blood. As the paper states "up to" 800 ml, the true total plasma drawn is likely to be less, and so the predicted fall per phlebotomy could be higher. The results are presented in Figure 3, below.

Figure 3 Impact on serum PFAS of plasma donation in Australian firefighters.

	PFHxS	PFOS	PFOA (approx.)
Baseline serum concentration (ng/ml)	5.2	11.7	1.1
Drop attributed to intervention (ng/ml)	1.5	3.1	0.8
% fall attributed to plasma donations	28.9	26.5	72.7
% fall predicted from one phlebotomy	1.47	1.35	3.7

Source: (Gasiorowski, et al. 2022)

An Italian intervention study provides some data on a small population with a high body burden of PFOA in particular (https://www.quotidianosanita.it/ 2017). For the group who participated in the plasma donation intervention, their baseline serum PFOA was 114 ng/ml. The authors reported that, "The average drop after four phlebotomy procedures from a starting serum median concentration of 113.6 ng/ml, of 40.1 ng/ml corresponds to a 35% drop from the initial value". Each procedure removed 616 ml of plasma so we can estimate that 4*616 ml is equivalent to 4*616/0.55 = 4480 ml of blood and so one normal phlebotomy would be predicted to have led to a reduction of 35*470/4480 = 3.7% reduction in serum concentration, consistent with the prediction from the Gasiorowski study for PFOA (Gasiorowski, et al. 2022).

Figure 4 Impact on serum PFAS of plasma donation in Italian population

	PFOA (approx.)
Baseline serum concentration (ng/ml)	114
Drop attributed to intervention (ng/ml)	40
% fall attributed to Plasma donations	35
% fall predicted from one phlebotomy	3.7

Source: (https://www.quotidianosanita.it/ 2017)

Models of likely benefit

Another approach is to model the likely benefit by predicting the reduction in blood serum concentration from the proportionate reduction in total body burden of PFAS. In pharmacology there is the concept of the volume of distribution (Vd). This is the apparent volume into which the total amount of a drug or chemical would need to be distributed to provide the same concentration as it currently is measured in blood plasma. For example, if you consume 200 micrograms of a compound and you measure the concentration in plasma as 0.025 micrograms/ml, then the Vd (the theoretical volume that gives you that concentration) is 200/0.025 = 8000 ml or 8 litres. More usually Vd is expressed as ml per kg body weight, given that it increases with the size of the person. For an adult weighing 70 kg in this example, that would be 8000/70 = 114 ml/kg body weight (bwt). The volume of distribution varies between chemical substances depending on how they distribute around the body.

For PFAS there are several different Vd estimates published. Widely used are estimates made a few years ago: 170 ml/kg for PFOA, 230 ml/kg for PFOS, and the same value as PFOS is assumed for PFHxS (Thompson, et al. 2010). A recent review drawing on several studies, however, concluded the estimates were 430 ml/kg for PFOA, 320 ml/kg for PFOS and 290 ml/kg for PFHxS (Chiu, et al. 2022). Conversely, work in Sweden, in the population studied for estimating half life (Li, et al. 2018), has measured rates of total excretion from urine and faeces, suggested lower values for Vd close to 100 ml/kg, although this work, as yet, is unpublished. Thus there remains some uncertainty of the exact value of Vd for these specific PFAS.

Applying these various Vd values from 100 to 420 to a 70 kg adult, we can estimate the expected reduction in measured PFAS from normal phlebotomy. Firstly, the concentration in plasma needs to be converted to whole blood. Most, but not all PFAS is stored in the plasma and the ratio of PFAS measured in serum or plasma to PFAS measured in whole blood averages 1.7 (Poothong, et al. 2017)Thus for a Vd of 420 ml/kg, removing 470 ml of whole blood would be expected to reduce the concentration measured in serum, by (470/1.7)/(420*70)= 0.9%. If the Vd is estimated to be 100 ml/kg the serum would drop by 4%. For someone weighing 50 kg, the estimated reductions would be a little higher ranging from 1.3 to 5.5%, whereas for someone weighing 90 kg the estimated reductions would be a little lower ranging from 0.7 to 3.1%. These estimated reductions for 50, 70 and 90 kg adults for two assumed values of Vd (420 and 100 ml/kg respectively) ranging from 1 to 5% are broadly in line with the results for phlebotomy and plasma donations intervention studies, summarised above, though possibly a little lower.

A further source of uncertainty concerns the rate at which PFAS distributes around the body. Following the removal of some PFAS from the blood, the concentration falls, then it rises again as

some of the PFAS stored in other organs in the body passed back to top up the blood again. This is shown for example in the Italian report where, immediately following the plasma donation the PFOA blood concentration fell steeply, but two to four weeks later the concentration had partly recovered. It is not known if that topping up was complete, as we do not know how quickly the PFAS can move between different body compartments, so it may be that if they had waited a little longer the overall apparent reduction might have been more limited. Measurements are needed later to demonstrate the overall net benefit, and this will need to be considered in the timing of the PFAS measurements to be made to assess reductions in persons who have received phlebotomy.

Further analysis and discussion

The findings from the two phlebotomy intervention studies are summarised in Figure 5, below.

Figure 5 Summary of the intervention studies.

	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	4.48	39.5	7.72	5.7	1.47
Australia (phlebotomy)	3.6	3.88	10.9	2.35	1.2	5.81

Source: (Genuis, et al. 2014), (Gasiorowski, et al. 2022)

From these intervention studies, the estimated benefit per phlebotomy procedure in terms of reductions in measured serum PFAS concentrations, ranged from 1.5% to 7.7%. Given all the evidence: from these two reports on therapeutic phlebotomy, the studies of blood donors, the experience of plasma donation and the male/female difference, there can be little doubt that phlebotomy would be expected to reduce concentrations of PFAS in blood. So it would be expected that individuals with raised PFAS in Jersey would experience a reduction, over and above that from normal body elimination rates, but there is uncertainty of the exact magnitude of the reduction. The indirect estimates of the likely benefit (from modelling and plasma donation studies) lie in the same range as the results from two phlebotomy intervention studies, summarised in Figure 5

It is also uncertain how average reductions across a population might apply to a given individual, as there is considerable variation in half-life from person to person. There is also uncertainty about the potential health benefits of such a reduction. For estimating the likely reduction per phlebotomy draw, it is reasonable to take an average of the various predicted percent reductions. The percentage reduction is not consistently different between PFAS or between high and low baseline levels, so if we assume the variation is due to chance, the average would be a reasonable estimate of the benefit from one treatment. This average (rounded) is a reduction of 4% per phlebotomy treatment. This would be in addition to the background reduction over time, which would be over a year on average, 12, 18 and 23% for PFHxS, PFOS and PFOA respectively. If blood were taken on 6 occasions over a year, the maximum benefit would be the accumulated impact of six 4% reductions, a total reduction of approximately 22%.

To illustrate this in actual concentration terms, we can estimate based on average trends in the studies summarised above, what that would mean for someone with a body burden for PFHxS associated with a serum concentration of 20 ng/ml over the course of a year. If they did nothing it would fall by 12% i.e., reducing by 2.4 ng/ml, to 17.6 ng/ml. If they had a phlebotomy procedure it

would fall by a further 4% to 16.8 ng/ml. If they had 6 phlebotomy procedures it would fall by 12% plus 22%, to 13.2 ng/ml.

It is important to note that everyone has some PFAS in their blood from various exposures, and the expected benefit is not so great if serum levels are close to the general background serum levels. If one's PFAS is only slightly raised above general population averages, then it would not fall by as much as 22%, due to the background exposure to PFAS from the general environmental and dietary exposure (Russell, Waterland and Wong 2015). This can be estimated by measuring PFAS in blood of people not next to a local source of contamination. Such a background average, would be the target final level for the phlebotomy procedure. It is impossible to reach a zero blood concentration given that it is impossible to avoid background exposure to PFAS. Figures for background blood levels are not available in Jersey directly, but one can get an estimate of the likely average background from other studies or through additional sampling.

A recent Europe-wide blood contaminants study (HBM4EU 2023) included PFAS, and the data can be openly consulted. Recent average background serum levels of PFAS are for PFHxS mainly in the range 0.2 – 0.5 ng/ml, for PFOA 0.5 – 1.5 ng/ml, and for PFOS 1 to 3 ng/ml. Therefore, for people with serum levels only a little higher than those values, the phlebotomy would give proportionately less benefit. The percent benefit would apply to the difference between the measured level and the background level. So, for example assuming a background of 3 ng/ml for PFOS, if someone's measured level was 9 ng/ml, the percent reduction would apply to the 6 ng/ml more than background that they have, so a 22% reduction would be 22% of 6 ng/ml (about 1.3 ng/ml), not 22% of 9 ng/ml (about 2 ng/ml).

In conclusion, the likely benefit of phlebotomy is estimated to be a 4% fall in serum levels for one procedure, 22% fall for six procedures, but less of a fall if the starting concentration was low and virtually no reduction expected as the concentration reaches the population background level.

Evidence from subject matter experts

Introduction

The Panel received evidence from three subject matter experts who have been involved in key studies that can help to inform the use of phlebotomy in managing PFAS load in the body. This added depth and context to the evidence obtained through the literature review and allowed for questions to be asked that arose from those studies. The subject matter experts were:

- **Professor Kristina Jakobsson, University of Gothenburg**: Physician Specialist in Occupational and Environmental Medicine and has been involved from 10 years ago in the Ronneby population exposed to firefighting foam as a clinician, as a health adviser to the Municipality from the healthcare system, and PFAS researcher exploring the health effects of PFAS in that community.
- **Professor Jonathan Martin, Stockholm University**: Professor at Stockholm University, working on PFAS since 2000, focuses on environmental analytical chemistry, and is a content matter expert in terms of environmental sources, the fate, and effects of PFAS. And he was a co-author in one of the intervention studies in the literature review.
- **Dr Roger A Klein, PFAS expert, Chemist and Medic**: Physical Chemist and Medic, working on PFAS for many years. Worked for over 50 years with the fire service and since 2000 in transitioning from fluorine containing firefighting foams to fluorine free firefighting foams and the environmental consequences and has been involved in a number of large legal cases. And he was a co-author in another of the intervention studies in the literature review.

Ronneby PFAS Research Program – Lessons learnt from clinical experience and research in Occupational & Environmental Medicine

Background

Ronneby is a small municipality in the south of Sweden, with a military airport that used PFOS since the mid-1980s. The PFAS pollution was discovered during the autumn of 2013 in the area of one of the two water works in the municipality, which was highly contaminated by PFAS. The airport was close to a situated in the middle of a large ground water reservoir, just a couple of kilometres away from the nearest waterworks, and the levels of PFAS in outgoing drinking water from the contaminated water works were high, with more than 10,000 nanograms per litre (sum of PFAS) at that time. The municipality immediately switched to the other water works, and everyone was provided with clean drinking water. The other water supply was minimally contaminated, with around 59 nanograms per litre at that time.

This initiated several local actions by the municipality, including within the healthcare system, it raised national interest, and a Commission of Enquiry was set up.

At the regional occupational and environmental clinic, a pilot investigation of PFAS levels in blood serum in school children found high levels, so it was decided that there was a need for widespread serum sampling in the community free of charge, in order to have a better monitoring of the exposure situation. The sampling included 3,500 people over 2 years. During this time, there was regular communication with the inhabitants in the municipality, and health and public health teams were kept informed.

While the background levels outside this municipality were about the same as background levels elsewhere in Sweden, it was found that those with high exposure and especially those living in the municipality during that time had very high levels with medians around 250ng/ml for both PFOS and

PFHxS, and some outliers at about 1800 ng/ml. About a third of the households had been highly exposed to contaminated water for decades. A significant number of people had total PFAS levels of 600ng/ml. It was noted that those residing outside the area with contaminated water had lower levels, but still above background, thought to be due to people not only drinking water from their homes, but also workplaces and the homes of others they visit.

Health effects described by Prof Jakobsson:

There have been very many epidemiological studies, some in highly exposed populations but mostly in background exposure ranges, looking at diseases, functional changes that are risk factors for disease, or functional changes happening in the body. There is a wealth of different health outcomes that have been studied. While evidence relating to kidney cancer, testicular cancer, and raised cholesterol seem to be relatively consistently shown in studies both at background levels and at high PFOA levels, but findings with regard to breast cancer, prostate cancer, pregnancy complication and thyroid disease are far less consistent.

Large scale group evaluations and 10 years of research in Ronneby show that several previously reported associations **at group level** between PFAS exposure and disease were confirmed, while some others were not. It was also clear that higher exposure levels did not result in proportionately higher observed risks for outcomes, e.g., birth weight and cholesterol levels. Finally, there were some new observations which need to be replicated in other studies before inferences can be drawn.

At individual level, it is clear that the risk of disease for any individual cannot be predicted by measured PFAS levels in the body. An important research focus in Ronneby is on early life effects, since PFAS can be passed to future generations during pregnancy and breastfeeding. However, on the subject of breastfeeding, Dr Jakobsson felt that there is a good argument that the overall benefit of breastfeeding for a child is clear, even where the mother has elevated PFAS levels.

Phlebotomy Treatment for Elimination of Perfluoroalkyl Acids in a Highly Exposed Family: A Retrospective Case-Series

Background:

This was a case study of a highly exposed family in Canada that was discovered Stephen Genuis (an environmental health clinician, who is interested in environmental exposures), and was a colleague of Professor Martin. Dr Genuis routinely asked his patients about their work history or their life history and would send plasma samples out for testing for environmental contaminants. He discovered a family of six with high exposure to PFOA, PFOS and PFHxS, and began an intervention study, the results below have been collated using the data from the study (Genuis, et al. 2014).

Context

This was a family of six people, the father who is 52, the mother who is 48, a son who is 23, a son who is 21, a daughter who is 18, a son who is 17 and a son who is 15.

The mother and father had their first son in 1985, a second son in 1987, and then they moved into a new house in 1989 and had three more children in that house. Because the house had a lot of carpeting, they thought it was a good idea to treat those carpets with 3M Scotchgard formulations, which was a stain repellent. You could hire companies to come in and treat the carpet in your home. They did that five years in a row when the house was quite new. They paused for about five years and then did more applications, the last ones in 2007 and in 2008. This is when the biological sampling was first done, and it was discovered they had quite high levels. The youngest children had the highest levels of exposure; possibly because they would have crawled around on the carpets

when they were very young, and it had been treated with Scotchgard and they also probably ingested more dust or had more hand to mouth activity and therefore got more of it in their body.

The family stopped treating their carpets with Scotchgard, replacing carpets with hardwood, and renovating to increase ventilation in their home, to make the air cleaner. They started phlebotomy in 2009.

Limitations to this study

Some limitations were identified that affect the extent to which any findings can be generalised. There were no experimental controls in this study because it was not an experiment. There was a comparator group from another study who were older people with historical occupation exposure, but there was concern that they were not an ideal comparator. The results may look quite different with a different comparator group.

Secondly, the participants are all from one family, so it is difficult to generalise or compare to broader populations or other groups of people.

Finally, it is a small study.

Summary of results/conclusions:

Notwithstanding the limitations outlined above, the intervention did appear to show benefit to the participants:

- Intermittent phlebotomy at rate similar to blood donation services appears safe and effective to facilitate removal of PFHxS, PFOS, and possibly PFOA.
- None of the participants described any ill effects of the phlebotomy.
- To balance some of the risks of phlebotomy a mineral supplement was taken.
- The Canadian Blood services prescribed that no more than 500 mills of blood be withdrawn every 56 days, and the family were under that, so this is a schedule that is quite a reasonable schedule if you are a regular blood donor.
- There was a 4-year intervention period.
- Clinical judgement in conjunction with informed patient consent should be used when considering interventions to facilitate removal of PFAAs.
- Weaker effect for PFOA may be real, or because baseline levels were closer to background levels.

It should also be noted that they did not completely eliminate the exposure. In 2008 a vacuum cleaner dust sample taken from the house showed high levels of PFAS PHOA and PHFxS. In 2012, the vacuum dust sample was taken again and showed the PFAS were still there, but they were nine to tenfold lower. Even at that level, however, ongoing exposure may have affected elimination. PFHxS, PFOS and PFAS all had relatively long biological half-lives.

The body burden of PFAS was mostly in the blood, so if you did remove blood, you would actually remove a significant fraction of the body burden.

Effect of Plasma and Blood Donations on levels of Perfluoroalkyl and Polyfluoroalkyl Substances in Firefighters in Australia

Background

This was a randomised clinical trial of firefighters in Victoria, Australia, with ethical approval. The point of the study was to look at whether blood donations or plasma donations were effective as a means of reducing PFAS levels in the blood. The background to this was a population of about 600

firefighters that had been tested for PFAS and two-thirds of those firefighters were over 29ng/ml. This is in excess of the “HBM II” level for PFOA and PFOS established by the Human Biomonitoring Commission of the German Federal Environment Agency as the level at which some form of intervention is deemed necessary. Some of the firefighters had blood levels of PFOS of 1400ng/ml, and two-thirds of the entire cohort were above HBM II.

Study approach

The study randomised participants into three groups: whole blood donation, plasma donation and a control group. Where blood or plasma were being taken, it was in accordance with blood products donation guidelines, therefore plasma was taken with greater frequency than whole blood. The 3 groups were sampled after 12 months, and again a few weeks after the intervention ended.

Study findings

The size of the study was constrained by available finance and each of the three arms in the study had approximately 100 participants. Both the phlebotomy and the plasma donation intervention groups showed a reduction in PFOS and a lesser reduction in PFHxS. In both cases, the reduction in the plasma donation group was greater than that in the phlebotomy group (possibly due to plasma donations being performed more times at shorter intervals). In both cases, there was a small increase in PFAS once the phlebotomy or plasma donation was stopped.

Risks and benefits of phlebotomy in the general population

Introduction

The most common cause for blood being taken in large quantities is the donation of blood for the benefit of other people in society. This altruistic donation is different in intent from therapeutic phlebotomy but involves very similar processes. Therapeutic phlebotomy is the name for taking blood in order to treat an illness or reduce the risk of a complication. It is most commonly used in conditions such as polycythaemia (where the body has too many blood cells which thicken the blood and risk complications, haemochromatosis (where the body has too much iron on board and it becomes toxic) and genetic conditions like sickle cell disease (where blood cells don't form properly) or porphyria (where certain toxins accumulate because a person doesn't have the mechanisms to break them down like most people do) (Assi and Baz 2014).

Risks from phlebotomy

Phlebotomy is an extremely safe procedure and the risks outlined below are either extremely rare, and minor or self-limiting, or both. The main potential risks from phlebotomy are (Newman 2004):

1) Physical Risks:

    a) Discomfort and pain: During blood donation, individuals may experience temporary discomfort and pain at the site of needle insertion. Although this is typically mild and transient, some donors may find it uncomfortable.

    b) Dizziness and lightheadedness: A common risk during or after blood donation is the onset of dizziness or lightheadedness. This can be attributed to a drop in blood pressure, which may occur due to the removal of a significant volume of blood.

    c) Haematoma and bruising: Occasionally, donors may develop a haematoma or bruise at the needle insertion site due to accidental damage to blood vessels during the procedure. While these complications are generally minor, they may cause discomfort and require symptomatic treatment.

    d) Arterial or nerve puncture: Damage to other structures in the area of the body from which blood is taken (the front of the elbow area, known as the antecubital fossa) is extremely rare, but it could result in severe bruising or even interruption of the blood flow to the lower arm if an artery is damaged, or nerve damage interfering with movement or feeling in the lower arm.

2) Infection risks:

    a) Needlestick injuries: Healthcare professionals who collect blood donations take precautions to ensure safe needle usage. However, there is always a small risk of needlestick injuries during the process, potentially exposing the donor to bloodborne infections such as HIV, hepatitis B, and hepatitis C. The likelihood of this happening is very low (Prüss-Ustün, Rapiti and Hutin 2005).

    b) Bacterial contamination: Although stringent hygiene protocols are in place and sterile, single use needles are used for blood donation, bacterial contamination of the needle could theoretically occur, leading to a potential risk of infection. The likelihood of this happening is very low.

3) Iron deficiency: Frequent blood donation can deplete the iron stores in the donor's body, leading to iron deficiency or anaemia. Iron is necessary for the production of new red blood cells, and a

significant loss without adequate replenishment can result in fatigue, weakness, and other symptoms associated with anaemia.

4) Psychological risks:

    a) Needle phobia and anxiety: Some potential donors may experience needle phobia or anxiety related to phlebotomy.

Risk factors and mitigation and prevention strategies

There are a range of characteristics which are associated with increased risk of complications from having blood taken. Some complications, such as fainting, and needle site problems are more common based on gender. Body weight, baseline blood pressure and pre-existing anaemia are also factors (Wiersum-Osselton, et al. 2014).

To address the risks associated with phlebotomy, the protocol for taking blood needs to ensure the following:

- Blood not being taken from persons who have a body weight below a predetermined threshold.
- Blood not being taken from anyone who have a blood pressure below predetermined threshold values.
- Blood not being taken from people whose haemoglobin is below a certain threshold level (anaemia).
- Proper needle insertion technique. Healthcare professionals are trained to follow proper protocols to minimize the occurrence of discomfort, pain, and complications such as hematomas, bruising, damage to nearby tissues and infection.
- Adequate rest and refreshments. After phlebotomy, people are advised to rest, hydrate, and consume a balanced meal to minimize the risk of dizziness and lightheadedness.
- Iron supplementation. To prevent iron deficiency, people may be advised to take iron supplements or increase iron-rich food intake.
- Ensuring that appropriate psychological support is available for those with needle phobia or other anxiety issues.

Potential wider benefits from phlebotomy

There is some evidence that when healthy people give blood, there are certain benefits to their health. This evidence is weak and insufficient to be important in decision-making but has been included here for completeness. A couple of studies have looked at whether phlebotomy can reduce liver damage in non-alcoholic fatty liver disease (a common illness of the liver) but it was not clear that there was real benefit (Kim and Oh 2016). Another small study (Zacharski, et al. 2008) looked at impact on cancer risk, and, while the findings are suggestive of a benefit, there is not enough evidence to draw any conclusions. Several other conditions have been mooted that might be prevented or improved by phlebotomy, but there aren't clinical studies to support that sufficiently. They include: Alzheimer's disease (Dwyer, et al. 2009) and heart disease (Houschyar, et al. 2012).

Types of clinical studies and their components

This report is considering the issues involved in offering phlebotomy to reduce PFAS body burden in people with past exposure and sections above have discussed the likely benefits in terms of PFAS reductions and potential risks associated with the procedure. As there are some uncertainties associated with estimating both the risks and benefits, if it is made available the Panel consider it should be carried out in the context of an intervention study where the phlebotomy and its impacts are carefully monitored in all participants. To put this in context it may be useful for readers to appreciate how this kind of study sits among the full panorama of clinical, epidemiological and intervention studies which are summarised in this section.

Clinical studies are important in advancing medical knowledge, improving people's health, and developing new treatments and therapies. These studies are designed to investigate various aspects of human health, ranging from understanding disease mechanisms to assessing the effectiveness, acceptability, cost-effectiveness and safety of medical interventions.

Types of clinical study

There are several different methodologies for conducting clinical studies; each having different strengths, weaknesses, and ethical considerations. Some of these are outlined below (Institute for Quality and Efficiency in Health Care 2016).

1. **Observational Studies**: Observational studies are designed to observe and analyse individuals in their natural settings without any intervention by the researchers. They aim to identify associations between certain variables, such as risk factors and health outcomes. Observational studies can be categorized into three main types:
    a) **Cohort Studies**: Cohort studies follow a group of people over a specific period, tracking their exposure to risk factors and monitoring their health outcomes. These studies help identify potential causes or risk factors for diseases.
    b) **Case-Control Studies**: In case-control studies, researchers compare individuals with a particular outcome (cases) to those without it (controls). By analysing past exposures or characteristics, researchers can determine potential associations between risk factors and diseases.
    c) **Cross-sectional Studies**: Cross-sectional studies collect data at a specific point in time to assess the prevalence or frequency of a condition or exposure in a population. They provide a snapshot of the population and help generate hypotheses for further investigation.
    d) **Case series**: Case series studies are a type of observational research design that provides valuable insights into rare or novel medical conditions, treatments, or interventions. In these studies, researchers collect and analyse data from a group of patients who share similar characteristics or have been exposed to a particular treatment. Unlike randomised controlled trials, case series studies lack a control group, making them less rigorous in establishing causality but highly informative in generating hypotheses for further investigation. Medical professionals often employ case series studies to explore the presentation of new diseases, adverse reactions to medications, or the outcomes of innovative treatments when randomised trials may not be feasible or ethical. (Mathes and Pieper 2017).
2. **Experimental Studies**: Experimental studies involve intentional manipulation of variables to assess the effects of interventions or treatments. These studies are often used to evaluate

the efficacy and safety of medical interventions. Experimental studies can be further divided into two main categories:

   a) **Randomized Controlled Trials** (RCTs): RCTs are considered the gold standard in clinical research. Participants are randomly assigned to different groups: an intervention group receiving the treatment under investigation and a control group receiving either a placebo or standard care. Ideally this is done on a "double blind" basis; where neither the participants nor the treating clinicians know whether an individual is in the intervention group or the control group. RCTs allow researchers to establish causal relationships between interventions and outcomes.
   b) **Non-Randomized Controlled Trials**: In some cases, randomisation may not be feasible or ethical. Non-randomized controlled trials assign participants to different groups based on other criteria, such as their location, age or clinical characteristics. While these studies have limitations, they can still provide valuable insights when randomised designs are not possible.

3. **Intervention Studies**: Intervention studies focus on assessing the effects of specific interventions or treatments on participants' health outcomes, clinical markers and/or biomarkers of exposure. These studies aim to investigate the potential benefits, risks, and optimal dosage or administration of interventions. They can be conducted as both experimental and non-experimental studies, including clinical trials and other controlled investigations. Such studies may or may not have comparison groups with different interventions, or a control group with no intervention. Healthcare service evaluations may also be interventional studies.
4. **Descriptive Studies**: Descriptive studies aim to describe the characteristics, patterns, and distribution of diseases or health-related events in populations. They often involve collecting data from medical records, surveys, or registries. Descriptive studies provide valuable information about the burden of diseases, risk factors, and potential public health interventions. They may also highlight areas for further study.
5. **Healthcare service evaluation**: Healthcare service evaluation studies play an important role in assessing and improving the quality and effectiveness of healthcare services. These studies are designed to analyse the various aspects of healthcare delivery, ranging from the accessibility and affordability of services to the satisfaction of patients and overall health outcomes. Researchers use a combination of quantitative and qualitative methods to gather data, often involving surveys, interviews, and clinical assessments. By scrutinising these findings, healthcare professionals and policymakers can identify strengths, weaknesses, and areas for enhancement in healthcare. (Moore, et al. 2015).
6. **Literature-based studies**: Literature-based studies are studies where scientific research that has been published in academic journals is analysed together so overall conclusions can be drawn. They are powerful methods of evidence synthesis in medical research that aim to summarise and evaluate the findings of multiple individual studies on a specific topic (Bello, et al. 2015).

   a) **Systematic reviews**: Systematic reviews involve a comprehensive and systematic search of the literature to identify all relevant studies meeting predefined inclusion criteria. Once selected, these studies are critically appraised for their quality, and their results are synthesised to provide a comprehensive overview of the evidence available.
   b) **Metaanalyses**: Meta-analyses take the process one step further by statistically combining the results of the included studies, providing a more precise estimate of the treatment effect or association between variables.

By pooling data from multiple sources, systematic reviews and meta-analyses increase the statistical power and generalisability of the findings, enabling researchers and healthcare professionals to draw more robust conclusions and make evidence-based decisions.

Components of clinical studies

The analysis above explores the different approaches to clinical study design, but there are common components or concepts that may be necessary regardless of the type of study. These include (Evans 2010):

- **A study protocol**: This is a written document that describes the purpose of the study, the study design, the methods that will be used, and the safety and ethical considerations.
- **Inclusion and exclusion criteria**: These are the criteria that participants must meet in order to be eligible to participate in the study. This can relate to a given illness or exposure to a given hazard, to the person's wider characteristics like age or gender, or to other characteristics that may impinge on potential risk or benefit.
- **Informed consent**: This is a process that explains the study and any risks, benefits and rights to potential participants. Participants must sign an informed consent form before they can participate in the study.
- **Data collection**: This is the process of collecting information about the participants, such as their medical history, their responses to the treatment, and any side effects they may experience.
- **Data analysis**: This is the process of analysing the data that was collected to determine the safety and effectiveness of the treatment.

The study protocol

A study protocol is the blueprint for a study and ensures that all aspects of the study are conducted in a consistent and ethical manner. A study protocol should include the following information:

- The purpose of the study
- The study design
- The methods that will be used
- The safety and ethical considerations
- The inclusion and exclusion criteria
- The informed consent process
- The data collection methods
- The data analysis plan

Ethical considerations in clinical studies

In any clinical study, there are key ethical considerations (Muthuswamy 2010). These Include:

1. **Informed Consent**: As alluded to above, one of the fundamental ethical principles in clinical studies is obtaining informed consent from study participants. Informed consent ensures that individuals fully understand the nature, purpose, risks, and benefits of the study before deciding to participate. Researchers have a responsibility to provide clear and

comprehensive information to participants, allowing them to make autonomous decisions. Informed consent must be voluntary, without any coercion, and participants should have the freedom to withdraw from the study at any time without penalty.

2. **Beneficence and Non-Maleficence**: The principles of beneficence and non-maleficence emphasise the obligation of researchers to maximise benefits and minimise harm to study participants. Researchers must carefully design studies to maximise potential benefits while minimising risks and adverse effects. Ethical considerations include selecting appropriate control groups, ensuring the validity and reliability of data collection, and monitoring participant safety throughout the study. If potential risks outweigh the expected benefits or if harm occurs during the study, researchers have an ethical obligation to halt the study and prioritise participant well-being.
3. **Privacy and Confidentiality**: Respecting privacy and maintaining confidentiality are crucial ethical considerations in clinical studies. Participants' personal information, medical records, and study data must be kept confidential to protect their privacy and maintain trust. Researchers must adhere to strict data protection protocols, use anonymised data whenever possible, and ensure that only authorised individuals have access to participants' personal information. Safeguarding privacy is not only a legal requirement but also an ethical imperative that promotes respect for individuals and upholds their dignity.
4. **Equitable Participant Selection**: Equity in participant selection is essential to avoid biases and ensure fair representation in clinical studies. Researchers should strive to include diverse populations, including individuals of different ages, genders, races, and socioeconomic backgrounds, to ensure the generalisability of study findings. Exclusion criteria must be scientifically justified and not based on discriminatory factors. Ethical considerations also involve addressing any potential power imbalances between researchers and participants and promoting inclusivity in the research process.
5. **Risk-Benefit Assessment**: Clinical studies must undergo rigorous risk-benefit assessment before initiation. Researchers must carefully evaluate the potential risks and benefits associated with the study and weigh them against alternative approaches. The risks should be minimised to the greatest extent possible, and the potential benefits should outweigh the potential harm. Ethical considerations include regular monitoring of participant safety during the study and prompt reporting of any adverse events to relevant authorities.

Ethical considerations in clinical studies are essential to protect the rights, safety, and well-being of study participants. For this reason, most studies will need to undergo ethical scrutiny from an external body, either an institutional ethics committee or a national or regional one.

The importance of sample size in clinical studies

Sample size determination is crucial for ensuring adequate statistical power in a clinical study. Statistical power refers to the probability of detecting a true effect when it exists. By including an adequate number of participants, researchers increase the power of their study, enabling them to detect smaller, yet clinically meaningful, differences between treatment groups. A small sample size may result in insufficient power, leading to a higher likelihood of false-negative results and missed opportunities for identifying effective interventions. Therefore, a larger sample size enhances the ability to detect significant treatment effects accurately (Evans 2010).

The generalisability of study findings, or external validity, is contingent on an appropriate sample size. In clinical research, it is essential to ensure that the sample is representative of the target population to generalize the results to a larger group of individuals. A small sample size may not adequately capture the heterogeneity (differences) present in the population, leading to limited

external validity. By increasing the sample size, researchers can enhance the representativeness of the sample, increasing the generalisability of the study findings and their applicability to a broader population. For this reason, a study with a smaller sample size is usually less influential scientifically that a similar study with a larger sample size.

Sample size also influences the precision of statistical tests and the width of confidence intervals. Statistical significance is determined by the p-value, which measures the probability of obtaining the observed results by chance alone. A larger sample size increases the precision of estimates leading to narrower confidence intervals. Consequently, it becomes easier to determine whether the observed results are statistically significant or due to random variation. A small sample size can result in wider confidence intervals and decreased precision, which may lead to inconclusive findings or overestimation of treatment effects.

Several factors influence the determination of an appropriate sample size. These factors include the research question, study design, desired effect size, expected variability, statistical power, and available resources. Researchers must carefully consider these factors to strike a balance between practicality and statistical robustness. Consulting statisticians and utilising power calculations can aid in sample size estimation and ensure that the study has sufficient power to detect clinically meaningful effects.

Generally speaking, cohort studies or studies that contain a control group need to be larger than things like case series or healthcare evaluation studies (Mathes and Pieper 2017), so it is not always practicable to conduct an RCT. This can be a particular issue with smaller effect sizes, rarer conditions or smaller populations.

Discussion

The evidence and evaluation

With relatively few, small studies having been published, the evidence of effectiveness of phlebotomy in limited. On the basis of the evidence available it is difficult to conclusively prove the magnitude of the effectiveness of phlebotomy using statistics, but there does seem to an effect on body burden of PFAS (although there is no direct evidence to suggest that this affects symptoms or disease risk). Studies to date are encouraging and there may be a case for a pilot programme with robust data collection.

Other potential interventions are out of scope of this review because the lead time to any delivery would be considerably longer, the potential risks from the intervention are expected to be higher, or the available evidence is even more limited. Other blood product extraction interventions, such as plasma donation, may permit more frequent intervention but may be less effective per intervention. Some drugs are being evaluated in intervention trials underway in other countries. When the Panel comes to evaluate those in full in review 3, it will be important to weigh the speed of overall effect against the degree of inconvenience for the person.

Areas of uncertainty

There appears to be a large variation in background elimination rates of PFAS among individuals. There is also a variation in reduction in body burden from person to person during phlebotomy interventions. It is not entirely clear what the drivers of this are. Gender differences (with faster elimination in women of childbearing age) have been hypothesised to relate to menstrual blood loss and due to childbirth.

The Panel has not yet looked systematically at the potential risks of PFAS, but it may be that it is difficult to quantify any specific benefit in health terms. This will become more clear after reviews 2 and 3. The percentage reduction in the chance of developing cancer or hypercholesterolemia or other issues from lowering PFAS body burden may not have been quantified and, because the studies on phlebotomy to date focus on body burden rather than health outcomes, it is unclear what the health benefits might be of a phlebotomy intervention. Longer term engagement and data collection could be important in establishing health benefits.

Priority or risk groups

The issue of the potential of mother to child transmission in pregnancy or during breastfeeding was highlighted by the subject matter experts. Some compounds are potentially hazardous to unborn children and to infants than to adults and older children. Given that phlebotomy in pregnancy is not often done, and that pregnancy is often not known about for some weeks, it was suggested that priority might be considered for women of childbearing potential. It was also noted that the Human Biomonitoring Commission of the German Environment Agency recommended lower PFAS levels for women of childbearing potential.

There was not specific evidence available about other population groups where the risk might be different.

Intervention levels

The German Environment Agency, through its Human Biomonitoring Commission (HBM), established HBM-II values; serum concentrations at which risk from human exposure to PFAS can't be excluded. These are: Women of child-bearing age: 5 ng PFOA/ml; 10 ng PFOS/ml; Other population groups: 10 ng PFOA/ml; 20 ng PFOS/ml (Schümann, Lilienthal and Hölzer 2021). The Panel explored whether

these were appropriate threshold levels for a phlebotomy programme and how evidence-based the levels were. There was a consensus that to set levels higher than HBM-II for phlebotomy might be problematic. The non-linear association between PFAS levels and some risk factors that Professor Jakobson showed support this approach. In the USA, the National Academy of Science (NAS) takes a different approach – looking at overall serum levels across several PFAS analytes and taking the sum, They suggest a total PFAS concentration of 20 ng/ml to be associated with risk in most individuals and that more vulnerable persons may be at risk at between 2 and 20 ng/ml (Committee on the Guidance on PFAS Testing and Health Outcomes 2022). When discussing intervention levels, the Panel were mindful that the primary analyte of concern in Jersey was PFHxS, for which there is no HBM-II level, and therefore the NAS approach to adding up individual PFAS analytes, including PFHxS, might be more helpful. The 7 analytes included in NAS approach are MeFOSAA, PFHxS, PFOA (linear and branched isomers), PFDA, PFUnDA, PFOS (linear and branched isomers) and PFNA, which are all in the list of analytes in the human biomonitoring (blood analysis) conducted on Jersey. PFHpS was also detected in the blood analysis and may also be considered.

The practicalities of phlebotomy

The Panel was generally comfortable with the safety of phlebotomy and were content with it potentially being part of an evaluation around reduction in PFAS body burden. In the light of the reduced effectiveness of phlebotomy as the population background PFAS levels are approached, the Panel were of the view that it would be wise to assess those background levels in Jersey. This could potentially be done anonymously, by looking at donated blood from elsewhere in Jersey. This would report far quicker than wider population testing and therefore would cause less delay to the starting of any phlebotomy programme.

There was a discussion around who might not be suitable for phlebotomy and the consensus was that the starting point would be the same criteria as for altruistic blood donation but there might be some flexibility on the basis of clinical judgement, given that the intent of phlebotomy in this instance, is to benefit the donor, so the balance of risks and benefits for that person are different than for an altruistic donation. Current guidance for altruistic donation has a minimum body weight of 50kg and an age range of 17-65 years. It was felt that, in this instance, clinical judgement could be used to vary those factors, as well as frequency and potentially even volume of blood taken.

There were discussions about what testing might be done and what else might be measured as part of a programme. Things like full blood count and body iron were considered important in assessing future phlebotomy, PFAS levels would be important for any evaluation, and things like cholesterol levels and measurements of quality of life may give an indication of any wider benefits of such a programme.

Finally, there was a discussion about selection of a suitable laboratory for PFAS testing and how that might be determined going forward. Several potential laboratories have been identified and will be investigated further.

Recommendations

In the light of the evidence and subsequent discussions, the Independent Scientific Panel on PFAS makes the following recommendations:

1. **The Panel recommends that the States of Jersey offer a programme of therapeutic phlebotomy for residents affected by PFAS as an interim measure pending detailed review of the health effects of PFAS and the effectiveness of different types of potential interventions.**
2. **That therapeutic phlebotomy be offered to those people who would like to take it up, were tested as a part of the public health programme in July 2022 and who were found to have a total across 8 measured PFAS compounds of at least 10 nanograms per millilitre of blood serum. Those eligible should receive information explaining the expected impact of phlebotomy so they can make an informed choice about participation in the service.**
3. **That background levels of PFAS in the wider community be estimated by the analysis of altruistic blood donation samples, excess serum collected to perform other tests, or by other means. This should be done on an anonymous basis.**
4. **That when an individual's serum PFAS levels reach the median background levels, further phlebotomy should not be performed.**
5. **That phlebotomy be offered to eligible people between 18 and 65 who weigh at least 50 kg. If an eligible person is not between 18 and 65 years of age or weighs less than 50 kg, clinical judgement should be applied as to whether it is appropriate for them to have phlebotomy.**
6. **That if an otherwise eligible person is pregnant at any point during the programme, they are not offered phlebotomy.**
7. **That if an eligible person has abnormal test results such as blood count or body iron or has concurrent illness, whether they are fit to participate in the phlebotomy programmes should be a matter of clinical judgement.**
8. **That, by default, phlebotomy should be offered every 2 months with a maximum volume of 480 ml withdrawn no more than 6 times in a year, but intervals could be increased or blood draw volumes reduced on the basis of clinical judgement about a specific individual.**
9. **That there should be ongoing testing before, during and after the programme to include:**
    a. **PFAS levels, including the 8 specific PFAS compounds detected in the first measurements in at least some individuals – PFHxS PFOS PFOA PFHpS PFNA PFPeS PFDA MeFOSAA**
    b. **Full blood count**
    c. **Iron studies**
    d. **Cholesterol**
    e. **A rating of the severity of any symptoms that were present prior to the programme**
    f. **EQ5D-5L or similar tool as a measure of overall quality of life**
    g. **A record of any adverse effects experienced during the programme**
10. **That a clinical history, including any activities that may have lowered PFAS levels (such as blood donation, taking medications like cholestyramine or probenecid and reproductive history) be taken from every participant.**

It should be noted that in Report 3, on the treatment and testing of people exposed to PFAS, recommendations will be made as to whether anyone not included in the previous testing programme should be tested and what treatments might be appropriate if they have elevated levels.

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Glossary

3M	a large manufacturer of chemical substances, including PFAS.
AFFF	aqueous film-forming foams; used in firefighting, particularly where liquid fuel may be involved. Can contain PFAS.
Anaemia	a condition where there is a lower than normal number of healthy blood cells. This can reduce oxygen availability and leea to shortness of breath and fatigue.
BMJ	British Medical Journal.
Body burden	describes the amount of chemicals in the human body.
bwt	Bodyweight.
C8	The name given to the surfactant PFOA in some commercial contexts, the name deriving from it having an 8 carbon length structure. Fluorosurfactants known as C8
CDC	Centers for Disease Control, a national public health body in the US.
EPA	Environmental Protection Agency, the federal agency in the US responsible for protecting the environment.
EQ5D-5L	European 5 dimension, 5 level, quality of life assessment. A commonly used tool to assess health related quality of life.
EU	the persistence of the chemical is described by its half-life, the time it takes for the concentration in the body or the environment to reduce by 50%.
FDA	Food and Drug Administration, the regulator of medicines in the US.
haematoma	localised bleeding outside blood vessels.
half-life	The time it takes for the concentration of a substance in the body or in the environment to reduce to half its initial value
HBM	Human Biomonitoring Committee of the German Environmental Agency.
Kg	Kilograms.
mean	a statistical average where all values are added up and divided by the number of readings.
median	a statistical measure where the middle value of a list of findings is used.
MeFOSAA	N-Methylperfluorooctanesulfonamidoacetic acid.
millilitre (ml)	one thousandth of a litre.
ml/y	millilitre per year.
nanogram (ng)	one billionth of a gram.
ng/ml	nanogram per millilitre.
NHS	National Health Service.
NICE	The National Institute of Health and Care Excellence, the national clinical guidelines organisation in England.
OECD	The Organisation for Economic Cooperation and Development, an international organisation comprising the countries with advanced economies.
PFAS	per- and polyfluoroalkyl substances.
PFCAs	perfluoroalkyl carboxylic acids or perfluoroalkyl carboxylate.
PFDA	perfluorodecanoic acid.
PFHpS	perfluoroheptane sulfonic acid.
PFHxS	perfluorohexane sulfonic acid.
PFNA	perfluorononanoic acid.
PFOA	perfluorooctanoic acid.
PFOS	perfluorooctane sulfonic acid.
PFPeS	perfluoropentane sulfonic acid.
PFSAs	perfluoroalkane sulfonic acids or perfluoroalkane sulfonates.
PFUnDA	perfluoroundecanoic acid.

plasma	the liquid portion of the blood.
Plume	the geographical area over which a contaminant spreads.
Scotchgard	a waterproofing and stainproofing treatment developed by 3M.
serum	the liquid that is left when blood has clotted, often used for doing medical tests.
Therapeutic phlebotomy	withdrawal of blood to prevent or cure disease.
UK	United Kingdom.
Volume of Distribution (Vd)	the theoretical volume into which an amount chemical or drug would be dispersed to result in the observed concentration in serum or plasma. Usually expressed in volume per body weight ml/kg.
WHO	World Health Organization, the United Nations agency devoted to health and health protection.

Appendix 1 – Minutes of Panel meetings

Minutes of the first public meeting of the PFAS Scientific Advisory Panel on Teams 10.00 – 11.30 am on Thursday 15th June 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 Plus support staff

Welcome and Introductions

Dr Steve Hajioff welcomed the panel members, and observers of the meeting including members of the public and the media to this first meeting, via Teams, of the PFAS Scientific Advisory Panel. The Panel consists of 3 Panel experts, and the panel were joined by Grace Norman from Public Health.

All panel members and guests introduced themselves and gave a brief overview of their roles and experience.

The Panel will produce 5 separate reports, which will look at academic literature reviews, studies, and assess the conclusions. The order of the reports was not an indication of the order of importance but following a logical cadence.

- Report 1 – is different to the other 4 as it will be an interim report, on therapeutic phlebotomy, subject to review.
- Report 2 – Current state of knowledge on the health effects of PFAS,
- Report 3 - Look at all potential clinical interventions (including reviewing therapeutic phlebotomy). Also, evidence on testing of PFAS levels.
- Report 4 – PFAS in the environment and how it can be managed.
- Report 5 – Reviewing any additional evidence available to update earlier reports.

The over-arching approach would be public facing, with a small amount of private deliberation in situations like cases of medical confidentiality or using experts who wish to remain anonymous.

The public meetings would include actions from the private meetings.

The final report would include testimonies, as long as anonymity can be maintained.

In addition, larger public meetings, for discussions on planning approaches for reports, launch of reports and any public consultation work, would take place.

The importance of interaction with observers and other stakeholders was acknowledged. There will shortly be a new PFAS mailbox for all queries and questions, particularly around

things discussed at meetings, and for people affected by PFAS, to express an interest in giving evidence to the panel. All comments would be welcome.

The public meetings will be recorded, anyone wanting the recording of this meeting would need to request it by e-mailing the publichealth@gov.je mailbox.

Declarations of Interest
No commercial declarations of interest from the panel.

Minutes and Matters arising
This is the first meeting, so no minutes or matters arising.

Additional findings from last meeting
None as this is the first meeting.

Discussion and approval

Planning for the first interim report on therapeutic phlebotomy

Summary of literature search so far
No formal literature search conducted yet by the panel. Dr Fletcher shared slides in the meeting regarding published work on phlebotomy and other procedures to reduce PFAS in the blood, including studies in Italy, a community in Sweden, firefighters in Australia and a family in Canada.

Points to note:

- PFAS studies have highlighted exposure to PFAS from many different sources and products, for example old fabric protection spray cans (as seen in the Canada example), and in food packaging, with the phasing out of many consumer products which contained PFAS in recent years this has resulted in a drop in PFAS levels generally in the population over the last 20 years.
- PFAS is everywhere in the environment at low levels and environment levels are reducing slowly.
- Will focus on Therapeutic Phlebotomy for the first interim report 1, however, other treatments will be explored in report 3.
- If phlebotomy is taken up, it is good to have documented data.
- As part of process to feed into the report there will be an assessment of the general benefits and risks of Phlebotomy. It will be important to present a balance of risk approach; particularly when some processes may not be safe.

General considerations for clinical studies
Dr Hajioff outlined that he designs and organises clinical studies in a variety of areas elsewhere, and that considerations may include:

- Understanding of effectiveness of studies.
- Whether a study would be appropriate to build around, i.e., the sample size of a study is important.
- Inclusion criteria, who is chosen to be involved in a study and understanding the implications.

- Exclusion criteria, for reasons of safety or the interventions would not make much difference for example.
- Evaluation of studies.
- Generalisability, assess extent to which they apply in Jersey.
- Exploring the chemicals to which people have been exposed.
- Whether there is a control group, i.e., one group where something is done and another group where nothing is done, to compare. There are complicated and ethical considerations with this.
- If the panel did recommend phlebotomy, what measurements would we need? – existing studies are relevant and look at if it would be meaningful in the Jersey context. Some studies have very small numbers and should not raise expectations of what low numbers can offer in terms of research value. There may be scope to work with other small studies elsewhere.

Subject Matter Experts and experts by experience

Views of subject matter experts would be sought for the next meeting and the panel will also seek experts by experience and personal experiences of those using therapeutic phlebotomy, including anyone at this meeting. Alternatively, observers at the meeting may have recommendations for subject matter experts. Please e-mail publichealth@gov.je

The Panel will collectively search for experts for the next meeting.

Draft Structure of 1st Interim report

Draft structure of the 1st report, will pull together 3 reviews for consideration at next meeting, along with any expert testimony:

- To what extent does phlebotomy work.
- Risks of phlebotomy.
- How might a study work.

Information

Any other business

A reminder was given that a recording of the meeting can be requested by e-mailing the Public Health mailbox.

Dr Fletcher's slides can be shared if they could not be seen in the meeting, please request them by e-mailing the Public Health mailbox at publichealth@gov.je

Actions:

- 2 reviews from literature to develop.
- 1 report on how studies are designed.
- Identification of experts to give evidence.

Date of next meeting

7th July 2023 – 10.00 to 11.30

The chair thanked the guests and panellists, and the meeting was closed.

Minutes of public meeting of the PFAS Scientific Advisory Panel on Teams
10.00 – 11.30 am on Friday 7th July 2023

Panel Members present:	Dr Steve Hajioff – Independent Chair Dr Tony Fletcher – PFAS and Health member Prof Ian Cousins – PFAS and Environment member
Subject Matter Experts present:	Dr Roger Klein, PFAS Expert, Chemist and Medic Professor Kristina Jakobson, University of Gothenburg Professor Jon Martin, Stockholm University
In attendance:	Grace Norman – Deputy Director Public Health 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 first report is interim report on feasibility of therapeutic phlebotomy as a way of lowering PFAS levels in the body
- 2nd report – more detailed, on health effects of PFAS
- 3rd report – more detailed, and will look at all potential treatments for PFAS, as well as looking at other interventions and testing
- 4th report – 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 and, being mindful that not all of the meeting observers would necessarily have been at the first meeting, gave a summary of their experience and expertise:

Steve Hajioff, Panel Chair – background as a physician and a retired Director of Public Health in an area of London with two major international airports and a variety of other environmental challenges.

Tony Fletcher, Panel Member - Epidemiologist 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.

Ian Cousins, 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 human 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. The Chair confirmed he was happy for Grace to participate in the Q&A as it will give sufficient breadth of answers to support writing of the report, but this will not compromise the independence of the report.

Support staff, for administration and minute taking, were also in attendance.

The Chair also welcomed subject matter experts to today's meeting, and asked them to introduce themselves:

Professor Kristina Jakobsson, University of Gothenburg:
Physician Specialist in Occupational and Environmental Medicine and got involved in the Ronneby case almost 10 years ago as a clinician, as a health adviser to the Municipality from the healthcare system, exploring health effects of PFAS, and became a PFAS researcher exploring the health effects for the Municipality.

Professor Jonathan Martin, Stockholm University:
Professor at Stockholm University, working on PFAS since 2000, focuses on environmental analytical chemistry, and is a content matter expert in terms of environmental sources, the fate, and effects of PFAS.

Dr Roger A Klein, PFAS expert, Chemist and Medic:
Physical Chemist and Medic, working on PFAS for many years. Worked for over 50 years with the fire service and since 2000 in transitioning from fluorine containing firefighting foams to fluorine free firefighting foams and the environmental consequences and has been involved in a number of large legal cases.

Declarations of Interest:
None.

Minutes of last meeting:
The minutes of the last meeting were taken as read and agreed, with no matters arising.

Actions from the last meeting were agreed at a private meeting after the public meeting, as follows:

- Literature review on phlebotomy led by Tony and Ian
- Descriptive writing on the structure and components of a clinical study by the Chair
- Review of risks to individual of phlebotomy – informational piece by the Chair

All three actions are currently in progress, and it is important not to finalise the first and third actions until after this meeting, as additional issues might be identified. However further information regarding this will be available at the next public meeting on 4th August.

Discussion
The Chair invited subject matter expert guests to present to the meeting, to inform the interim report 1 on therapeutic phlebotomy.

Professor Jakobsson shared a presentation titled “Ronneby PFAS Research Program – Lessons learnt from clinical experience and research in Occupational & Environmental Medicine.”

Summary notes from the presentation:

- No information on phlebotomy as this was not considered as an intervention;
- Ronneby is a small municipality in the very South of Sweden, with a military airport that used PFOS since the mid-1980s;
- The pollution of PFAS was discovered during the autumn of 2013 in the area of one of the two Water Works in the municipality, which was highly contaminated by PFAS;
- The municipality immediately switched to the other water works, and everyone was provided with clean drinking water;
- About a third of the households had been highly exposed to contaminated water for decades;
- The airport was in the middle of a large ground water reservoir, just a couple of kilometres from the main airport, the levels of PFAS in outgoing drinking water from the contaminated water works was high, with more than 10,000 nanograms per litre at that time;
- The other municipality was minimally contaminated, with around 59 nanograms per litre at that time.

This initiated a lot of local actions from all areas of the municipality, including the healthcare system, it raised national interest, and a Commission of Enquiry was set up.

At the regional clinic, a pilot investigation of PFAS levels in serum in school children found high levels, so it was decided that there was a need for open serum samplings in the community free of charge, in order to have a better monitoring of the exposure situation. The sampling included 3,500 people over 2 years. During this time, there was a lot of communication with the inhabitants in the municipality, and health and public health were kept informed.

While the background levels outside this municipality were about the same as background levels elsewhere in Sweden, it was found that those with high exposure and especially those living in the municipality during that time had very high levels with medians around 250, but outliers about 1800 nanograms per litre. Quite a lot of people had PFAS levels of 600 nanograms per litre and about similar for the hexane sulphonate, but much lower for PFOA. It was noted that those who had left the area with contaminated water had lower levels. No exact information was available from the general population, as water is drunk in many different places, such as work, visiting friends and relatives in other areas.

<u>Health effects:</u>
There have been lots of epidemiological studies, mostly in background exposure ranges, looking at diseases, functional changes that are risk factors for disease, or functional changes happening in the body. There is a wealth of different health outcomes that have been studied.

Strengthening evidence has been found for PFAS and causal effects regarding kidney cancer, testicular cancer, cholesterol, but weakening evidence for PFAS and causal effects regarding breast cancer, prostate cancer, pregnancy complication or thyroid disease.

Summary of risk at group level:
Large scale group evaluations and 10 years of research clearly shows that on the individual level it is not likely that specific disease could be attributed to exposure. Their work also did not show a linear dose-response at higher PFAS levels.
Working within clinical contexts, there is surety that the specific levels of PFOS in the body of the person cannot predict the risk of disease for that individual. There are no clear links. Research focus is now on early life effects, and whether pregnant women can pass on PFAS to future generations. There are no restrictive recommendations on breastfeeding, and there is an argument that the benefits of breastfeeding might be even more beneficial for a child with prenatal PFOS exposure.

The Chair thanked Professor Jakobsson for her presentation.

Professor Martin shared a presentation with the meeting titled “Phlebotomy Treatment for Elimination of Perfluoroalkyl Acids in a Highly Exposed Family: A Retrospective Case-Series.” He invited anyone who wished to contact him for further information to e-mail him at jon.martin@aces.su.se

Professor Martin explained this was a case study of a highly exposed family in Canada that was discovered by a colleague of his Stephen Genuis, an environmental health clinician, who has been really interested in environmental exposures. He routinely asked his patients about their work history or their life history and would send plasma samples out for testing for environmental contaminants. He discovered a family of six with high exposure to PFOA, PFOS and PFHxS, and began an intervention study, the results communicated in this paper have been collated using the data from the study.

Background:
This was a family of six people, the father who is 52, the mother who is 48, a son who is 23, a son who is 21, a daughter who is 18, a son who is 17 and a son who is 15.

The mother and father had their first son in 1985, a second son in 1987, and then they moved into a new house in 1989 and had three more children in that house. Because the house had a lot of carpeting, they thought it was a good idea to treat those carpets with 3M Scotchgard formulations, which was a stain repellent you could hire companies to come in and treat the carpet in your home. They did that five years in a row when the house was quite new. They paused for about five years and then did more applications, the last ones in 2007 and in 2008. This is when the biological sampling was first done, and it was discovered they had quite high levels. The youngest children, had the highest levels of exposure, and the reason that they have the higher level of exposure is that when they were born, they were crawling around on the carpet in their home, when it had been treated with Scotchgard and they probably ingested more dust or had more hand to mouth activity and got more of it in their body.

They stopped treating their carpets with Scotchgard, replacing carpets with hardwood, and renovating to increase ventilation in their home, to make the air cleaner. They started phlebotomy in 2009.

Summary of results/conclusions:

- There was a 4-year intervention period.
- Intermittent phlebotomy at rate similar to blood donation services appears safe and effective to facilitate removal of PFHxS, PFOS, and possibly PFOA.
- None of the participants described any ill effects of the phlebotomy.
- Weaker effect for PFOA may be real, or because levels were closer to background levels.
- Clinical judgement in conjunction with informed patient consent should be used when considering interventions to facilitate removal of PFAAs.
- They did not completely eliminate the exposure.
- In 2008 a vacuum dust sample taken from the house showed really high levels of PFAS PHOA and PHFxS.
- In 2012, the vacuum dust sample was taken again and showed the PFAS's were still there, but they were nine to tenfold lower.
- PFHxS, PFOS and PFAS all had relatively long biological half-lives. If you remove the exposure entirely, you would expect half of PFHxS to be eliminated in 8 to 9 years, PFOS to be 5 years and 3.8 years for PFOA.
- The body burden of PFAS was mostly in the blood, so the volume of distribution was such that if you did remove blood, you would actually remove a significant fraction of the body burden.
- To balance some of the risks of phlebotomy a mineral supplement was taken.
- The Canadian Blood services prescribed no more than 500 millilitres of blood be withdrawn every 56 days, and the family were under that, so this is a schedule that is quite a reasonable schedule if you are a regular blood donor.

<u>Limitations to this study</u>

- It is a small study.
- The participants are all from one family, so it is difficult to generalise or compare to broader populations or other populations.
- There were no experimental controls because it wasn't an experiment.
  There was a comparator group from another study who were older people with historical occupation exposure, but there was concern that they were not an ideal comparator.
- The results may look quite different with a different comparator group.

The Chair thanked Professor Martin for his presentation.

Dr Klein gave a presentation titled "Effect of Plasma and Blood Donations on levels of Perfluoroalkyl and Polyfluoroalkyl Substances in Firefighters in Australia."

This was a randomised clinical trial of firefighters in Victoria, Australia, with complete ethical approval. It was a fairly limited study, but it does align with what would you have just seen from the Canadian family study. The point of the study was to look at whether blood donations or plasma donations were effective as a means of reducing PFAS levels in the blood.

The background to this was a population of about 600 firefighters that had been tested for PFAS and two-thirds of those firefighters were over 29 nanograms per millilitre. The significance of this is that 29 nanograms per millilitre PFOS is the so called HBM 2 level established by the Human Biomonitoring Commission of the German Federal Environment Agency as the level at which some form of intervention is deemed necessary. Some of the firefighters had blood levels of PFOS of 1400 nanograms per millilitre, and two-thirds of the entire cohort were above HBM 2.

It is important to note the difference between PFOS and PFHxS is not as simple as it sounds.
Commercial PFOS, as was present in Scotchgard treatments or in firefighting foams, always had about 5 to 8% in purity of PFHxS, so if you were exposed to what you thought was PFOS, you were also being exposed to be PFHXs, and possibly others.

With water drinking levels, PFOA is defined as less toxic than PFOS, but the reverse is true. If there are higher levels, there is a noticeable risk. PFHxS and PFOS decay at different times, so over a 30-year period some levels will remain higher.

If you are looking at interventions for reducing blood levels, it's a question of triage. Realistically, it should be done if it is between HBM1 and HBM 2 levels.
They need to look at the mode of exposure and reduce exposure as much as possible.

The publications from the German Federal Environment Agency are available in English for information.

Within the last three or four years, just before the pandemic, the UN Stockholm Convention, Persistent Organic Pollutants Review Committee classified PFAS, PFOS and PFOA as persistent organic pollutants. The general conclusions were that PFHxS were considerably more toxic than PFOS.
The problem is that if you have been exposed to PFOS, let's say from firefighting foam or the use of Scotchgard, you will also have been exposed to PFHxS.

Phlebotomy does have a role to play, however, plasma donation is potentially more effective. One of the issues is how often you can take blood and who from. Guidelines for blood donation say over 50 kg in weight, and aged 17-65 which will exclude teenagers, children, and many women.

The chair noted plasma donation will form part of report 3, but for the purposes of this report, we are only looking at therapeutic phlebotomy.

The clinical randomised study involved the regular taking of blood by phlebotomy and the taking of plasma at regular intervals, and then the 3 groups were sampled at the end of the first year. The data is fairly limited as was this was a fairly small study with financial constraints. Each group, 1) the control group, 2) the Blood Donation group, and 3) the Plasma Donation Group had just under 100 participants.
What we see is with PFOS there is a fairly small drop in the blood donation group and the same is true of PFHxS, which is barely significant. However, plasma donation is more effective.
One question addressed in the study - what happens when you stopped blood donation or plasma donation? What we saw was a small uptake in the blood levels.

The Chair thanked Dr Klein for his presentation.

Question and Answer summary

A question-and-answer session then followed, summary points to note:

- Different studies show different elimination levels;
- There can be a huge difference in removal rates for individuals;
- Difficult to statistically prove the success of phlebotomy;
- Cannot explain the majority of differences in individuals, for example, women lose blood through menstruation and childbirth, and there are other unknown elements;
- No issues raised with phlebotomy generally;
- A question of contaminated bore hole water, dilution and trigger levels globally was raised. In Jersey, there has been confirmation from Jersey Water that bore holes in the effect area are not currently feeding the mains water supply.

Summary of actions

- To pull together the content of the discussion and presentations and use it to develop the report and to feedback at next meeting on 4 August.
- To feedback on the 3 reviews at the next meeting: 1) literature review on phlebotomy, 2) a written piece on the structure of a clinical study and 3) a review of risks to individuals to giving blood.

The next meeting is scheduled for 4 August.

The Chair thanked everyone for attending the meeting and reminded anyone with any comments or queries to e-mail the Public Health mailbox publichealth@gov.je and they will be brought to the chairs attention.

There being no further business, the meeting was closed.

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.

Draft minutes of public meeting of the PFAS Scientific Advisory Panel on Teams 10.00 – 12:00 on 6th September 2023

Panel Members present:	Dr Steve Hajioff – Independent Chair Dr Tony Fletcher – PFAS and Health member Professor Ian Cousins – PFAS and Environment member
In attendance:	Grace Norman – Deputy Director Public Health Plus support staff

Welcome:
The Chair welcomed everyone to the Panel meeting in public, and reminded people the meeting was 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:

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

The chair mentioned that people could email the panel at pfaspanel@gov.je.

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. He 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: A 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.

Declarations of Interest
No additional declarations.

Minutes of last meeting
Agreed.

Matters arising
None.

Additional findings since last meeting
The Chair and Scientific Advisory Panel attended the **PERFORCE3 PFAS symposium and FLUOROS 2023, in Germany** last week (organised by Professor Ian Cousins) and met a number of experts who will be able to help inform the reports being produced by this Panel. This also gave an opportunity to speak again with the experts who had presented to the Panel previously.

Grace Norman gave an updated presentation titled “PFAS Blood Test Results” regarding the testing of Islanders last year. This took into account the results not previously available when presented to Islanders in December (at that time all the results were not in). The meeting noted there were difficulties in interpreting results due to no approved methodology or scientific agreement regarding interpreting blood test results.

Grace Norman gave an overview of the process:

- Referral from GP
- Triaged by Public Health about whether they met the eligibility criteria
- Appeals process
- Blood sampled in July 2022 – Islanders given a choice of 9 or 35 analytes to be tested
- Results to Islanders provided through GP to support with interpretation of what the results mean

The eligibility criteria were:

- Lived (or worked) in plume area 1991-2006 for 1 (or 2) years, AND
- Regularly consumed water from private water supplies, AND
- Have 1+ symptom consistent with health concerns described in the literature, AND
- Have a GP referral

There was an expectation they were over 18 years old. There was no clear definition of the plume area, but Islanders who live or had lived in the west of the island were included. No Islanders were excluded based on geographical eligibility.

Summary of blood test results:

- 88 results
- 10 different PFAS analytes were detected
    - 3 analytes (PFHxS, PFOS, PFOA) were detected in all samples tested
    - 7 analytes were detected in some samples but not others (shown in table)
    - The remaining 25 analytes were not detected in any of the samples

A summary table was presented:

Analyte	Number of Samples with Detectable Concentration	Number of samples	Percentage of samples analyte detected in
PFHxS	88	88	100%
PFOA	88	88	100%
PFOS	88	88	100%
PFNA	59	88	67%
PFHpS	43	75	57%
PFPeS	5	75	7%
MeFOSAA	<5	88	Less than 5%
PFDA	<5	88	Less than 5%
PFBA	<5	75	Less than 5%
PFHpA	<5	75	Less than 5%

A comparison was made to results from a US population study, the only one known about at the time of the analysis, as follows:

- A “threshold” was taken from the USA population results (the upper 95th percentile)
- The Jersey results were compared to this threshold, to see whether they fell above or below it
- 4 analytes were above the threshold in over 10% of Jersey samples (in yellow)

Analyte	Reference Population NHANES*		Results from Jersey Samples	
	Average (95% CI)	Threshold	Number (%) of Jersey samples above 95th percentile of reference population ^	
PFHxS	1.08 (0.20-1.18)	3.7	70	80%
PFOS	4.25 (3.90-4.62)	14.6	26	30%
PFHpS	0.22 (0.18-0.26)	1	15	20%
PFOA	1.42 (1.33-1.52)	3.77	16	18%
PFNA	0.41 (0.36-0.46)	1.4	<5	<5%
PFHpA	Unavailable	0.2	<5	<5%
MeFOSAA	0.20 (0.18-0.21)	1	0	0%
PFDA	0.19 (0.18-0.21)	0.6	0	0%
PFOSA	Unavailable	< LOD	0	0%
PFUnA	0.13 (0.12-0.14)	0.4	0	0%
PFPeS	Unavailable	Unavailable	0	0%

Grace Norman was thanked for her presentation.

Grace Norman mentioned that there is a report on the results being developed and will be shared in due course.

The Chair noted that it will be useful to know the threshold data on PFOS and PFOA.
Dr Tony Fletcher said it will be useful to see the sum of PFAS and see this grouping above the thresholds as agreed.

Dr Tony Fletcher asked about the eligibility criteria wording “symptom” and suggested it would be easier to say sign or symptoms and investigations. Grace Norman confirmed that this would have been more appropriate.

This helps to set the discussions in context. The Chair felt it was better not to have too much detailed data before they make their recommendations, to enable recommendations based on the science and for the Panel to have a purer discussion.

Developing the recommendations and timeline

- The completed draft and recommendations (for this report 1) to be presented at a public consultation event on 11th October.
- The second half of this event will be to look at the scope for report 2.
- The draft to then go to a brief public consultation.
- Panel to review, edit and release the final report in November *(or December, date to be confirmed).*

Headings for recommendations from the Panel:

1. Inclusion criteria, at what threshold levels of PFAS would phlebotomy be offered and when would it stop?
2. Exclusion criteria – who might not be suitable for phlebotomy. some of which will be left to the clinical judgement of those running the service
3. What blood tests should be done and what other data should be collected?
4. How often and how much blood taken?
5. Are there risk groups requiring additional attention?
6. Do we recommend such a programme or not?

Inclusion criteria – PFAS levels

Prioritising people with higher levels of PFAS; if you are close to background levels there is less risk to exposure and less gain from phlebotomy. The German HBM *(Human Bio Monitoring)* II value is 20 ng/ml (*nanograms per millilitre)* can be a starting point for the general population (PFOS) and 10ng/ml (PFOA). HBM levels are lower for women of reproductive age at 10 ng/ml (PFOS) and 5 ng/ml (PFOA).

The Panel have not found a measure for measuring total PFAS. However, do have some additional analyte information. The challenge with using HBM levels is that they only include PFOA and PFOS and don't take account of PFHxS, which is an important analyte in the Jersey results. The National Academy of Science (NAS) cover wider PFAS substances and wrote about a sum of wider PFAS *(adding up the results for the different analytes),* stating that there is understood to be 'no risk to health' below 2 ng/ml and an 'increase of risks to health' above 20 ng/ml.

The options for inclusion criteria for the Panel to recommend include 1) the HBM levels *(only reflects PFOS and PFOA)*, 2) the NAS levels, or 3) the Panel can look at something different to either of those. Professor Cousins noted the precautionary guidelines set out in the NAS report suggesting concerns at low levels.

Dr Tony Fletcher suggested looking at applying the NAS approach using the sum of PFAS as a screening tool and then take in to account the HMB values, and include people whose total PFAS value is over 10ng/ml. This could be a cut-off point (the sum of PFAS not just one substance) and would make it more available and inclusive (not withstanding exclusions to individuals). Therefore, 10 ng/ml for either sex with no differentiation for childbearing women.

To help move the decision-making process forward, the Chair asked if the Panel want to use a higher level of 20ng/ml for a threshold for phlebotomy? The answer was no. Therefore, the Panel are looking at HBM or lower for the inclusion criteria. Dr Tony Fletcher said that consideration should be given to including those who have not already been tested. The panel have assumed that the only people offered phlebotomy at present *(if agreed)* will be the 88 who were tested last year *(July 2022)*.

It was explained that the panel could recommend wider testing before launching the programme, but this would delay the programme for the people who have already been tested.

The Chair asked the Panel if they want to look at a wider population at this time. The Panel felt they would want to know more about the size of the affected population in the plume area. The Panel could recommend that the Government of Jersey consider offering a phlebotomy programme for others who met the other criteria but were not symptomatic at that time. It makes sense for report 3 to cover this which will look at testing of the broader population and other modes of interventions.

The Panel discussion explored a range of levels. The recommended thresholds may cause a problem as if the Panel follow NAS, it should include a sum above 2ng/ml which would be a lot of people at the population level. This may be closer for HMB I (lower risk) and could be a risk of adverse effects between 2-20 ng/ml in 'sensitive' populations (although it was not clear what the definition of 'sensitive' was). The Panel have not yet reviewed health effects. There is 'increasing concern' up to 20 ng/ml. The NAS report was a consensus across a wider range of stakeholder's opinions, so including all concerns rather than looking specifically at the risk to health based on published literature.

PFOA and PFOS levels being stricter for women seems to make sense (in the German HBM levels, *because of the potential for harm associated with childbearing)*. The Panel could look at general figures for the general population being 20 ng/ml cut-off. The Chair then asked is it lower than this?

HBM do not recommend criterion for PFHxS, which is one of the analytes that is highest in the affected population. The Panel could say 20 ng/ml for everyone and consider lower for vulnerable groups (including women of childbearing age).The Chair was initially thinking that appropriate levels would be 20ng/ml for the majority of the affected population and 10 ng/ml for women of childbearing potential, but the Chair is comfortable with Dr Fletcher's suggestion of using total PFAS at greater than 10ng/ml which is a compromise (looking at the evidence).

The recommendation is to offer the intervention to anyone identified in the testing pilot with a total PFAS (in blood serum) sum of greater than 10 ng/ml.

This is in the region of other studies where phlebotomy has been used, e.g., the Australian study.

This recommendation is made with the caveat to look at how the NAS got to their recommendation in report 3. This evidence can inform a longer-term offer in the future. The NAS report concludes whilst phlebotomy can be effective, no specific recommendations on the use of phlebotomy or levels are included.

It was suggested that the stop level would be at background level and establish the background level in the Jersey population by testing donated blood samples from elsewhere on the Island (anonymous samples). The population background level would be the stop criteria. Twice the background level is probably the point where the impact of phlebotomy would be undetectable.

The recommendation is when an individual's PFAS levels reach the background level in the programme, they would no longer be eligible for the intervention.

Exclusion criteria

An age range of 18-65 years and minimum body weight of 50kg is applicable for altruistic blood donation. Therefore, the Panel could take a different view for the criteria and look at clinical judgement on this criterion.

The programme lead or Haematologist would input into other clinical criteria i.e., blood pressure, iron levels and haemoglobin. Depending on whether the blood results were abnormal or normal the clinical lead would decide if a person continued with the programme. It was felt it would not be appropriate to exclude individuals just because they didn't meet the criteria for altruistic donation and that input from a specialist would be appropriate, because, unlike altruistic donation, there is the potential for benefit for the individual in therapeutic phlebotomy, which changes the risk profile:

1. Under 18 years old - defer to clinical judgement
2. Over 65 years old –defer to clinical judgement
3. Pregnancy – not usually done in pregnancy, exclude on the basis of safety
4. Body weight cut-off – leave to clinical judgement (could take less blood for people below 50kg)

In summary, it was agreed all except pregnancy should be left to clinical judgement.

It was suggested to test haemoglobin and iron levels as indicator to ensure that individuals are well enough to continue phlebotomy, also test cholesterol given the association with PFAS, check PFAS levels in testing and discuss what PFAS to test for. Symptom scoring and wellbeing score, for example, EQ-5D-5L *(a self-assessed, health-related quality of life questionnaire)* could also be used.

It was hoped all PFAS tests could be done by the labs. Professor Cousins was confident labs can test a number of analytes. The Chair suggested 7 analytes to test. Also, to check the cost implications and proportionality of this.

The recommendations were:

- PFAS levels should be monitored, including the ones found most commonly in the affected population
- Haemoglobin and blood iron to be measured regularly
- Cholesterol measured regularly
- Scorings of symptoms recorded, and quality of life score monitored

Frequency and volume
For altruistic donation there is a difference between donation time for men and women for a standard 480ml donation. However, in altruistic donation there is no benefit to the individual. The Panel discussed if the amount donated should this be the same, or down to clinical judgement.

The Chair suggested a frequency of every 2 months for everyone, and clinical judgement needed if this is too frequent. Also, the Panel could look at 2 monthly but a smaller volume for women (the volume can be varied). The need to be mindful of menstrual blood loss in women and changes in iron levels was also noted. The clinical lead would advise on issues for men and women (low weight, blood pressure etc).

The Panel suggested a pre-test (-1month), then a programme every 2 month, then testing, and discussed whether there is a need to confirm if using the PFAS test baseline or the -1month month test? The Chair said that the pre-test is mainly about safety to proceed. The blood tests from last year will be the marker for eligibility.

Recommendation: Default frequency of 1 blood draw every 2 months with clinical judgement as to whether this frequency or quantity is reduced and whether each intervention would go ahead.

Risk groups
The Panel had already discussed pregnancy and inclusion criteria above. The discussion included whether other risk groups should be left to clinical judgement. For example, if a heart condition made an individual more at risk. This will be picked up by clinical judgement.

Dr Fletcher said that regarding the potential reduction from phlebotomy, there is a big range of variability in natural excretion rates between individuals, and it would be interesting to know the natural excretion rate in the population. The Panel could compare the excretion rate with phlebotomy compared to the excretion rate in the population without phlebotomy. PFAS is held in proteins and plasma more than blood cells and held in other parts of the body and leaches out back to the blood (volume of distribution). It would be useful to know

excretion information from the participants, for the longer term and in the context of a global model to see the benefits of phlebotomy.

The Panel would like to consider taking additional samples from some individuals to plot the recovery period and the rate of the PFAS leaching back into the body. Consideration can be given to adding a research component and could consider compensation for people who may participate. The Chair said this would add some complexity to the delivery of the service and suggested this be revisited as part of a later report.

There may be scope to add additional monitoring at the end of the programme, or when people cease the therapeutic phlebotomy. It was agreed to look at the feasibility.

Recommendation: Additional testing should be undertaken 12 weeks after someone completes therapeutic phlebotomy.

Given that the starting point is using results from a year ago, it would be helpful to take a thorough clinical history which should include any interventions they have tried previously to reduce blood levels of PFAS, for example, blood donation and medicines.

The Chair said for the background levels he suggests using the subject matter expert suggestion to use anonymous sampling from other parts of the island and test them for PFAS to ascertain the Jersey background levels.

Do we recommend that Jersey proceed with a programme of phlebotomy to lower PFAS body burden in effected individuals and to gather data for further research?

Recommendation: Yes. Agreed by the Panel.

The Chair agreed to discuss separately with Public Health the need for a questionnaire, including capturing adverse risk and benefits of intervention.

Any other business

The Panel was reminded of the next steps in the process:

- To incorporate the recommendations from today's meeting into the draft report
- The draft report to go to the public event on 11th October
- The draft report to be subject to comments for 2 weeks after the public event
- Final report to be completed second half of November

Date of next meeting

The date of the next Panel meeting is 12th October, at 10am *(Online).*

The Chair thanked all participants and observers.

There being no further business, the meeting was closed.