

Risks and wider benefits of probenecid treatment

Probenecid is a uricosuric agent primarily used in the management of hyperuricemia associated with gout and gouty arthritis. It functions by inhibiting the renal tubular reabsorption of uric acid.

Safety and Tolerability of Probenecid

Most patients tolerate probenecid well, but some may experience side effects (Sattui & Gaffo, 2016).

Common Side Effects

- **Gastrointestinal Disturbances:** Nausea, vomiting, anorexia, and abdominal pain are the most frequently reported adverse effects.
- **Headache and Dizziness:** Mild to moderate headaches and dizziness may occur.
- **Flushing and Fever:** Occasionally reported in some patients (BOGER & STRICKLAND, 1955).
- **Drug Interactions:** Probenecid interacts with various medications, potentially altering their pharmacokinetics. These include some antibiotics, anti-inflammatory drugs, Methotrexate and HIV drugs (American Pharmacists Association & Inc, 2016).

Rare Side Effects

- **Renal Calculi (Kidney Stones):** Increased uric acid excretion can lead to stone formation in susceptible individuals (BOGER & STRICKLAND, 1955).
- **Aplastic Anaemia and Haemolytic Anaemia:** Rare haematological disorders have been associated with probenecid (NCBI, 2004)
- **Nephrotic Syndrome:** Cases of proteinuria and nephrotic syndrome have been reported (Hertz et al., 1972)
- **Allergic Reactions:** Skin rashes, pruritus, and, rarely, severe hypersensitivity reactions like Stevens-Johnson syndrome and anaphylaxis (Hillecke, 1965).

Capital and revenue requirements for prescribing probenecid to reduce PFAS body burden

Necessary Equipment

None

Required Personnel

Any doctor can prescribe probenecid and so the service could be delivered using existing resources in primary care. It should be noted, however, that probenecid is no longer licensed in the UK. While off-label drugs can still be prescribed, some doctors may not be comfortable so doing. Some training may also be required.

Maintenance and Regulatory Compliance

No additional requirement over the status quo

Cost of prescribing probenecid to reduce PFAS body burden

Capital cost

There are no capital costs

Additional Costs to Consider

- **Training:** There may be some training costs around the safe and appropriate prescribing of probenecid. While it is likely that this could be delivered within existing resources, it would be reasonable to assume an additional cost of £5,000 per annum.
- **Drug costs:** It is difficult to assess the costs of probenecid because, as an unlicensed medicine, it no longer has a list price in the UK (which is used as a proxy for Jersey pricing). Given that volumes will be relatively low and the costs of importation will increase the effective price, it is reasonable to assume a cost per patient per year of £800.

In summary

Bringing all of this together, there is zero capital outlay. Assuming that 50 people are treated and they require twelve months of treatment each, total drug costs would be £40,000. On this basis, the maximum total programme cost, if it were fully funded, would be £45,000 per annum.

American Pharmacists Association, & Inc, L.-C. (2016). *Drug Information Handbook: A Clinically Relevant Resource for All Healthcare Professionals*. Lexicomp.

<https://books.google.co.uk/books?id=-EgBkAEACAAJ>

BOGER, W. P., & STRICKLAND, S. C. (1955). PROBENECID (BENEMID): Its Uses and Side-Effects in 2,502 Patients. *A.M.A. Archives of Internal Medicine*, 95(1), 83-92.

<https://doi.org/10.1001/archinte.1955.00250070099012>

Hertz, P., Yager, H., & Richardson, J. A. (1972). Probenecid-induced nephrotic syndrome. *Arch Pathol*, 94(3), 241-243.

Hillecke, N. A. (1965). Acute Anaphylactoid Reaction to Probenecid. *Jama*, 193(9), 740-740.

<https://doi.org/10.1001/jama.1965.03090090046018>

NCBI. (2004). *PubChem Compound Summary for CID 4911, Probenecid*

<https://pubchem.ncbi.nlm.nih.gov/compound/Probenecid>

Sattui, S. E., & Gaffo, A. L. (2016). Treatment of hyperuricemia in gout: current therapeutic options, latest developments and clinical implications. *Therapeutic Advances in Musculoskeletal Disease*, 8(4), 145-159.

<https://doi.org/10.1177/1759720x16646703>

Risks and wider benefits of bile acid sequestrant therapy

Bile acid sequestrants are a class of medications primarily used to lower low-density lipoprotein cholesterol (LDL-C) levels in patients with hypercholesterolemia. They function by binding bile acids in the gastrointestinal tract, preventing their reabsorption, and promoting their excretion. This process leads to increased conversion of cholesterol into bile acids in the liver, thereby reducing serum cholesterol levels. In this instance, however, they would be being used to lower serum PFAS, and any reduction in total or LDL cholesterol would be an additional benefit.

The main agents in this class include cholestyramine, colestipol, and colesevelam. These medications have varying safety and tolerability profiles.

Cholestyramine

Cholestyramine is one of the earliest bile acid sequestrants introduced for clinical use. It is available as a powder for oral suspension, often requiring multiple daily doses (Jacobson et al., 2015)

Common Side Effects

- **Gastrointestinal Disturbances:** Constipation is the most frequently reported side effect, occurring in up to 50% of patients (Hou & Goldberg, 2009). Other GI symptoms include bloating, abdominal discomfort, nausea, and flatulence.
- **Interference with Nutrient Absorption:** Cholestyramine can impair the absorption of fat-soluble vitamins (A, D, E, K) and folic acid (Glueck et al., 1972). Long-term use may lead to deficiencies if not monitored.
- **Drug Interactions:** It can bind other orally administered medications, reducing their bioavailability. Drugs such as digoxin, warfarin, and thyroxine may have decreased efficacy (Gallo et al., 1965).

Rare Side Effects

- **Hyperchloremic Acidosis:** Particularly in children and patients with renal impairment (Kamar & McQuillan, 2015).
- **Bleeding Tendencies:** Due to vitamin K deficiency from prolonged use (Vroonhof et al., 2003).

Colestipol

Colestipol is available in granule and tablet forms. Similar to cholestyramine, it binds bile acids in the intestine.

Common Side Effects

- **Gastrointestinal Symptoms:** Constipation is also common, though some studies suggest a slightly lower incidence compared to cholestyramine (Lent-Schochet D, 2023) Other GI side effects include indigestion, nausea, and haemorrhoids due to straining.
- **Nutrient Absorption Interference:** Like cholestyramine, it can reduce the absorption of vitamins and some medications (Hameed MH, 2024).

Colesevelam

Colesevelam is a newer bile acid sequestrant with a high affinity for bile acids and is available in tablet and oral suspension forms. It has an advantage over the other agents in that it has been shown to improve glycaemic control in type 2 diabetes mellitus (Fonseca et al., 2008).

Common Side Effects

- **Gastrointestinal Effects:** Studies have shown that colesevelam has a lower incidence of GI side effects compared to cholestyramine and colestipol (Puleston et al., 2005). Constipation remains the most common, but occurs less frequently.
- **Drug Interactions:** Colesevelam can affect absorption of other medicines

Comparative Analysis of Side Effects and tolerability

Gastrointestinal Side Effects: Cholestyramine and colestipol have higher rates of GI side effects, particularly constipation, compared to colesevelam (Puleston et al., 2005). The severity of constipation and abdominal discomfort is often greater with cholestyramine due to its formulation and higher required doses (Insull, 2006).

Drug and Nutrient Interactions: Cholestyramine and Colestipol can both bind other drugs and reduce absorption of vitamins, necessitating careful timing of medication administration and possible supplementation. Colesevelam exhibits somewhat fewer interactions, potentially allowing for more flexibility in dosing schedules (Drugs.com, 2024).

Patient Compliance: Cholestyramine's powder form can be unpalatable, affecting adherence. Colestipol tablets and colesevelam tablets/suspension offer improved compliance (Brunetti & DeSantis, 2015). Colesevelam requires fewer daily doses, enhancing tolerability (Drugs.com, 2024).

Capital and revenue requirements for establishing and running a service to prescribe bile acid sequestrants to reduce PFAS body burden

Necessary Equipment

None

Required Personnel

Any doctor can prescribe bile acid sequestrants and so the service could be delivered using existing resources in primary care, Some training may be required.

Maintenance and Regulatory Compliance

No additional requirement over the status quo

Cost of prescribing bile acid sequestrant therapies to reduce PFAS body burden

Capital cost

There are no capital costs

Additional Costs to Consider

- **Training:** There may be some training costs around the safe and appropriate prescribing of bile acid sequestrants. While it is likely that this could be delivered within existing resources, it would be reasonable to assume an additional cost of £5,000 per annum.
- **Drug costs:** The estimated costs of the different bile acid sequestrants, in generic formulations are outlined below. These are per person per year estimates and do not include any discounts that might be available.

Medication	Daily Dose	Annual Cost (£)
Cholestyramine (Generic)	12 g (3 sachets)	£350.40
Colestipol (Generic)	10 g (2 sachets)	£438.00
Colesevelam (Generic)	3.75 g (6 tablets)	£730.20

In summary

Bringing all of this together, there is zero capital outlay. Assuming that 50 people are treated and they require six months of treatment each, total drug costs vary from £8,760 for cholestyramine to £18,255.50 for colesevelam. On this basis, the maximum total programme cost would be £23,255.50 per annum.

- Brunetti, L., & DeSantis, E. H. (2015). Patient tolerance and acceptance of colesevelam hydrochloride: focus on type-2 diabetes mellitus. *P t*, *40*(1), 62-67.
- Drugs.com. (2024). *Comparing Cholestyramine vs Colesevelam*. Retrieved 29 Oct from <https://www.drugs.com/compare/cholestyramine-vs-colesevelam>
- Fonseca, V. A., Rosenstock, J., Wang, A. C., Truitt, K. E., & Jones, M. R. (2008). Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care*, *31*(8), 1479-1484. <https://doi.org/10.2337/dc08-0283>
- Gallo, D. G., Bailey, K. R., & Sheffner, A. L. (1965). The interaction between cholestyramine and drugs. *Proc Soc Exp Biol Med*, *120*(1), 60-65. <https://doi.org/10.3181/00379727-120-30443>
- Glueck, C. J., Ford, S., Jr., Scheel, D., & Steiner, P. (1972). Colestipol and cholestyramine resin. Comparative effects in familial type II hyperlipoproteinemia. *Jama*, *222*(6), 676-681. <https://doi.org/10.1001/jama.222.6.676>
- Hameed MH, P. P., Farzam K. (2024). *Colestipol*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK587349/>
- Hou, R., & Goldberg, A. C. (2009). Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. *Endocrinology and metabolism clinics of North America*, *38*(1), 79-97.
- Insull, W., Jr. (2006). Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *South Med J*, *99*(3), 257-273. <https://doi.org/10.1097/01.smj.0000208120.73327.db>
- Jacobson, T. A., Maki, K. C., Orringer, C. E., Jones, P. H., Kris-Etherton, P., Sikand, G., La Forge, R., Daniels, S. R., Wilson, D. P., Morris, P. B., Wild, R. A., Grundy, S. M., Daviglius, M., Ferdinand, K. C., Vijayaraghavan, K., Deedwania, P. C., Aberg, J. A., Liao, K. P.,

- McKenney, J. M.,...Brown, W. V. (2015). National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *Journal of Clinical Lipidology*, 9(6), S1-S122.e121. <https://doi.org/10.1016/j.jacl.2015.09.002>
- Kamar, F. B., & McQuillan, R. F. (2015). Hyperchloremic Metabolic Acidosis due to Cholestyramine: A Case Report and Literature Review. *Case Rep Nephrol*, 2015, 309791. <https://doi.org/10.1155/2015/309791>
- Lent-Schochet D, J. I. (2023). *Antilipemic Agent Bile Acid Sequestrants*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK549906/>
- Puleston, J., Morgan, H., & Andreyev, J. (2005). New treatment for bile salt malabsorption. *Gut*, 54(3), 441-442. <https://doi.org/10.1136/gut.2004.054486>
- Vroonhof, K., van Rijn, H. J., & van Hattum, J. (2003). Vitamin K deficiency and bleeding after long-term use of cholestyramine. *Neth J Med*, 61(1), 19-21.

Risks and wider benefits of Psyllium husk treatment

Psyllium husk, derived from the seeds of the *Plantago ovata* plant, is a soluble fibre commonly used as a dietary supplement. It is used for its laxative properties and can be used in various gastrointestinal conditions, such as constipation and irritable bowel syndrome (IBS).

Additionally, dietary fibre such as that psyllium contains has been associated with beneficial effects on cholesterol levels and glycaemic control (Anderson et al., 2009).

Safety and Tolerability of Psyllium Husk

Psyllium tends to be well-tolerated, particularly if started at low dose and increased gradually and taken with plenty of water (McRorie, 2015).

Common Side Effects

- **Gastrointestinal Effects:** Psyllium is generally considered safe for most individuals when taken as directed. The most common side effects are gastrointestinal and include:
 - **Bloating and Wind:** Increased fibre intake can lead to bloating, flatulence, and abdominal discomfort, especially during the initial stages of consumption (Fernández-Bañares, 2006).
 - **Mild Stomach Cramps:** Some users may experience minor stomach cramps due to increased intestinal activity (Eswaran et al., 2013).

These symptoms typically subside as the body adjusts to the increased fibre intake.

Rare Side Effects

- **Allergic Reactions:** Although rare, allergic reactions to psyllium husk can occur. Such reactions range in severity from itching and skin issues through to life-threatening reactions like anaphylactic shock. Individuals with known allergies to psyllium or other members of the *Plantago* genus should avoid its use (James et al., 1991).
- **Oesophageal and Intestinal Obstruction:** Psyllium expands upon contact with water. If not taken with sufficient liquid, it can swell in the throat or oesophagus. Rare cases of intestinal blockage have been reported, particularly in individuals with pre-existing gastrointestinal disorders (Hefny et al., 2018). To mitigate this risk, it's essential to consume psyllium with at least 200ml of water.

Capital and revenue requirements for making Psyllium husk available to reduce PFAS body burden

Necessary Equipment

None

Required Personnel

None. Psyllium can be purchased over the counter

Maintenance and Regulatory Compliance

No additional requirement over the status quo

Cost of accessing Psyllium husk to reduce PFAS body burden

Capital cost

There are no capital costs

Additional Costs to Consider

- **Training:** There may be some training costs around the safe and appropriate prescribing of Psyllium. While it is likely that this could be delivered within existing resources, it would be reasonable to assume an additional cost of £5,000 per annum.
- **Drug costs:** The estimated costs of the different psyllium preparations are outlined below. These are per person per year estimates and do not include any discounts that might be available.

Product	Daily Dose	Annual Cost (£)
Generic Powder	7 g	£30.66
Fybogel Sachets	2 sachets (7 g)	£97.09
Psyllium Capsules	14 capsules (7 g)	£424.13

In summary

Bringing all of this together, there is zero capital outlay. Assuming that 50 people are treated and they require twelve months of treatment each, total drug costs vary from £1,533 for generic Psyllium to £21,206.50 for capsules. On this basis, the maximum total programme cost, if it were fully funded, would be £26,206.50 per annum.

Anderson, J. W., Baird, P., Davis, R. H., Jr., Ferreri, S., Knudtson, M., Koraym, A., Waters, V., & Williams, C. L. (2009). Health benefits of dietary fiber. *Nutr Rev*, 67(4), 188-205.

<https://doi.org/10.1111/j.1753-4887.2009.00189.x>

Eswaran, S., Muir, J., & Chey, W. D. (2013). Fiber and functional gastrointestinal disorders. *Am J Gastroenterol*, 108(5), 718-727. <https://doi.org/10.1038/ajg.2013.63>

Fernández-Bañares, F. (2006). Nutritional care of the patient with constipation. *Best Pract Res Clin Gastroenterol*, 20(3), 575-587. <https://doi.org/10.1016/j.bpg.2005.11.002>

Hefny, A. F., Ayad, A. Z., Matev, N., & Bashir, M. O. (2018). Intestinal obstruction caused by a laxative drug (Psyllium): A case report and review of the literature. *Int J Surg Case Rep*, 52, 59-62. <https://doi.org/10.1016/j.ijscr.2018.10.001>

James, J. M., Cooke, S. K., Barnett, A., & Sampson, H. A. (1991). Anaphylactic reactions to a psyllium-containing cereal. *Journal of Allergy and Clinical Immunology*, 88(3, Part 1), 402-408. [https://doi.org/https://doi.org/10.1016/0091-6749\(91\)90104-V](https://doi.org/https://doi.org/10.1016/0091-6749(91)90104-V)

McRorie, J. W., Jr. (2015). Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 1: What to Look for and How to Recommend an Effective Fiber Therapy. *Nutr Today*, 50(2), 82-89.

<https://doi.org/10.1097/nt.0000000000000082>

1. Approaches to testing and retesting individuals for human blood levels of PFAS

1.1 Introduction

Concentrations of various PFAS have been measured in plasma, serum, and whole blood, although serum is the most common choice for PFAS testing.[1] Serum PFAS levels are generally about twofold higher than in whole blood whereas plasma and serum levels are very similar.[2] Measured PFAS concentrations in human serum vary across different populations, from single- or double-digit nanograms per millilitre in the general population to thousands of nanograms per millilitre (ng/mL) in occupationally exposed workers and residents near contaminated sites.[1] In this section the focus is primarily on PFOS, PFOA and PFHxS as they are the PFAS commonly associated with AFFF contamination. There have been a large number (many hundreds) of studies testing PFAS levels in human serum worldwide and it is not necessary to review all those studies in detail here. There have already been several excellent reviews on PFAS serum levels in the general population and in highly exposed populations. [1, 3, 4] Other reviews specifically focused on occupational exposure to PFAS.[5, 6]

Testing of chemical contaminants in humans is a mature discipline and a book was written by the National Research Council of the National Academies (NRCNA) on the subject already in 2006.[7] Specific guidance on PFAS testing has also been published by the NRCNA more recently in 2022.[8] Regarding PFAS testing, the NRCNA 2022 report [8] recommends that “discussions about PFAS testing should always include information about how PFAS exposure occurs, potential health effects of PFAS, limitations of PFAS testing, and the benefits and harms of the testing”. Clinicians would usually follow the principle that they only order testing when they know how to interpret and act on the results. However, as we will conclude below, in contaminated communities PFAS testing of serum is seldom done for clinical management purposes, but rather to understand the PFAS exposure and effects for research or for legal purposes.

1.2. Testing and retesting in populations with elevated levels of PFAS

As mentioned above, a review published in 2015 already covered testing in populations with elevated levels of PFAS.[3] The findings of that review will be briefly summarized here. Interestingly, the 2014 review totally neglected exposure related to the use of AFFF at commercial airports and military bases. The reason for this omission was that studies reporting elevated exposures related to AFFF use have all been published in the last decade, i.e. after 2015. Considering that to date there is no review on the elevated PFAS serum levels related to AFFF use, the known studies are summarized below.

1.2.1. Testing and retesting in non-AFFF related exposure scenarios

In addition to releases from use of AFFF, several other environmental releases of PFAS have reached surface and/or groundwater sources for drinking water. Depending on location, these other types of environmental releases can be described as: (1) industrial emissions from nearby PFAS manufacturing plants; (2) landfill leachate releases; and (3) run-off from sewage-sludge amended agricultural fields. Testing for PFAS in each affected community demonstrated concentrations above levels reported in the general population. [3]

Emissions of PFAS from the 3M Cottage Grove manufacturing facility as well as leaching from several local landfills resulted in elevated levels of PFAS in public and private wells in the East Metro communities of the Minneapolis-St. Paul metropolitan area.[3] A random sample of East Metro citizens in the affected areas had their serum tested for PFAS. In 2008, the geometric mean serum concentrations for PFOS (35.1 ng/mL), PFOA (15.1 ng/mL), and PFHxS (8.2 ng/mL) were

approximately three to four times higher than the 2007–2008 National Health and Nutrition Examination Survey (NHANES) data for the general population. [3] In a retesting of this population 2 years later, the geometric mean serum concentrations for the East Metro area declined in line with the serum elimination half-lives for these substances. [3] Based on these percentage declines, it was concluded that the exposure reduction efforts appeared to be working but continued serum testing was warranted to ensure further declines occurred. [3]

PFAS-contaminated wastewater from the 3M manufacturing plant in Decatur, Alabama was treated at a wastewater treatment facility which resulted in the generation of PFAS-contaminated sewage sludge.[9] Subsequent application of the PFAS-contaminated sewage sludge to agricultural land resulted in PFAS contamination of surface waters and private wells. [9] The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a human exposure investigation in which a total of 85 households participated (153 people volunteered from these households) in serum testing for PFAS. [10] Geometric mean serum PFAS concentrations in the contaminated area were approximately two to five times higher than in the reference group. [10] The range of serum PFOS concentrations for those people consuming private well water were (in parentheses): PFOS (38.6–472 ng/mL), and PFOA (7.6–144 ng/mL) and PFOS (6.1–59.1 ng/mL), which is much higher than the general population. [10] An epidemiological study was also performed on the population. [10] Retesting of some members of same population (n=45 volunteers) in 2016 showed a decline in serum concentrations.[11]

Elevated PFOA serum concentrations were found in the population living in proximity to the DuPont Washington Works fluoropolymer (i.e. Teflon) manufacturing plant (near Parkersburg, West Virginia).[12] Serum testing was originally conducted by Emmett et al. [12] on a limited scale before a large-scale serum testing effort (69,030 individuals tested over a 13-month period) was undertaken as part of a class-action lawsuit.[13] The overall geometric mean PFOA concentration was 32.9 ng/ml compared to 3.9 ng/L for NHANES at the time (2003-2004). [13] One of the six water districts sampled (Little Hocking) had a much higher PFOA mean concentration of 227.6 ng/ml (>50 times higher than NHANES). [13] This large-scale serum testing was part of a set of well-known epidemiological studies (C8 Panel). Bartell et al.[14] retested the blood of 200 residents of the Little Hocking and Lubeck water districts over an 18-month time frame to monitor potential declines in serum levels after water filtration was implemented. They estimated the average serum PFOA decline was 26 % per year resulting in a median serum PFOA half-life of 2.3 years. A number of other research projects were also set up by the C8 Science Panel and involved retesting on individuals in the contaminated area,[15] but these are not connected to clinical management. Furthermore, the C8 Medical Monitoring Program (<http://www.c-8medicalmonitoringprogram.com/index>) was created as part of the settlement of the class action lawsuit by DuPont. Settlement Class Members were entitled to medical monitoring paid for by DuPont. The C8 Medical Monitoring Program recommended medical screening every 3 years following the initial medical screening. In the initial screening they underwent a medical examination and provided a serum or urine sample for PFAS testing. Retesting of PFAS levels in serum or urine was offered as part of the 3-yearly follow-up medical screenings. As the C8 Medical Monitoring Program is linked to a class action lawsuit, the motivation for retesting is different compared to other contaminated communities managed by local health authorities.

Levels of fluoroethers (e.g. hexafluoropropylene oxide dimer acid, HFPO-DA or GenX) and “other PFAS” were tested in serum samples (289 adults and 55 children) of Wilmington, North Carolina residents who live downstream of a fluoropolymer manufacturing plant.[16] It was believed that the primary drinking water source of Wilmington was contaminated by the plant. Here, only the results

of the “other PFAS” are summarized as they are most relevant for Jersey. Concentrations of PFHxS, PFOA, PFOS and PFNA were detected in most ($\geq 97\%$) participants and their levels were higher than U.S. national levels for the 2015–2016 National Health and Nutrition Examination Survey. [16] Median levels of the sum of 5 PFAS (PFOS, PFOA, PFHxS, PFNA and PFHpA) in the adults were 20.8 ng/ml. Retesting was done on 44 participants and the median percentage decrease for the four legacy PFAS (PFOA, PFOS, PFHxS, and PFNA) ranged between 0% and 13%. [17]

Application of sewage sludge to agricultural land near Arnsberg, Germany led the large-scale contamination of a drinking water reservoir. [18, 19] Disposal of contaminated sludge from the paper industry was identified as the source of the contamination. A serum testing study was conducted of a sample of residents from Arnsberg (men and mothers/children) with reference populations selected from nearby populations. Blood samples were tested in 2006 [18] and blood was retested in 2007 [19] and 2008 [20]. In 2006, the geometric mean PFOA plasma concentrations (in parentheses) were: children (23.4 ng/mL); mothers (23.6 ng/mL); and men (30.3 ng/mL). [18] These geometric mean and concentrations were approximately five times higher than in the reference populations. Two years later after the remediation efforts, the geometric mean PFOA plasma levels declined by 39 % (children and mothers) and 26 % (men) in the Arnsberg population compared to 13–15 % in the reference groups. [20]

Elevated serum concentrations of PFAS were reported in the serum from commercial fishermen on the Tangxun Lake in Wuhan China. [21] The fishermen ate the fish they caught on a regular basis. Fluorochemical manufacturing plants in an industrial park upstream from the wastewater treatment plant situated on the upper reaches of the lake were identified as the PFAS contamination source. PFOS serum concentrations (for 37 Tangxun Lake fishermen, 7 family members, and 9 reference individuals) were 10,400 ng/mL, 3,540 ng/mL, and 19 ng/mL, respectively. [21] The highest serum PFOS concentration measured was 31,400 ng/mL in a commercial fisherman, [21] which is the world record PFOS serum concentration, and three times higher than the next highest value reported, in a 3M production worker.

In Belgium, a first investigation that tested blood levels (800 participants) of PFAS in people living within a 3 km radius of the 3M Chemicals factory in Zwijndrecht (Antwerp Province) was undertaken and revealed elevated levels of PFAS (especially PFOS) in 9 of 10 people sampled. The results of the 2021 blood tests will be further investigated and linked with medical data. In the summer of 2022, an additional 5 km population study started where 40,000 blood samples were taken in an area up to 5 km from 3M. In addition, the Youth Study on Human Biomonitoring was also started near 3M, in which more data on lifestyle, eating habits and health were measured and monitored in a selected group of young people. All of the abovementioned studies in Belgium will allow building new knowledge on the health risks of PFAS exposure in this region. In this case the initial testing within 3 km of the factory led to a follow up testing programme which was larger (40,000 instead of 800 participants) and more widespread geographically (5 km from the factory instead of 3 km).

In Veneto, Italy high levels of PFAS contamination have been found and associated with the activity of an industrial plant located in Trissino, in the province of Vicenza. The Miteni Group (formerly called Rimar), a fluorochemical manufacturer which has produced PFAS since 1968, was identified as being responsible for the pollution. [22] The human population in the region had been exposed to elevated levels of PFAS through the consumption of PFAS contaminated drinking water. In 2016, a biomonitoring study was conducted [22] on two randomly selected groups of people 20–51 years of age: 257 subjects living in the contaminated area and 250 living in a background area not affected by the contamination incident. The results showed that those living in the contaminated area had significantly higher serum PFAS concentrations than the control group had and that participants

residing in municipalities served by contaminated waterworks had the highest serum PFAS concentrations. To address public concerns about exposure to PFAS, a health surveillance program started in January 2017 and continues for the prevention, early diagnosis and treatment of chronic disorders possibly associated with PFAS. Blood (and urine) testing for 12 PFAS was offered to the entire highly exposed population of 105,000 people, which makes this study unique. Data were also collected through a structured interview on socio-demographic characteristics, personal health history and lifestyle habits. A preliminary study of 18,345 participants born between 1978 and 2002, 14–39 years of age at recruitment was published in 2020,[23] but recruitment continued. The population is being recruited for a second round, including retesting of blood and urine for PFAS, which started in September 2020. By February 2022, 55,597 individuals were recruited (60,5% of invited) in the 1st round, and 2,623 in the 2nd round. The median PFAS serum concentrations for PFOA, PFOS and PFHxS were recently reported to be 36.8 ng/mL, 3.8 ng/mL and 3.7 ng/mL, respectively.[24] The program includes a thorough assessment of individual exposure as well as behavioural and clinical risk factors for cardiometabolic disorders, providing tailored counselling for exposure and risk reduction, and the referral of subjects with altered biomarkers for subsequent diagnostic and therapeutic evaluation.

1.2.2 Testing and retesting in AFFF-related exposure scenarios

In addition to Jersey, elevated human serum levels related to AFFF use have been observed at 11 locations in the US,[25, 26] 1 location in Sweden,[27] 3 locations in Australia [28] and 1 location in Denmark. (ref) Here we briefly review the different serum testing strategies used in these 16 known locations that have elevated PFAS serum levels related to historical AFFF use.

In Jersey, a programme of free-of-charge serum testing was arranged in 2022 for people who had lived in the affected areas between 1991 and 2006, regularly consumed contaminated borehole water from the affected areas, and had symptoms consistent with conditions that have been associated with PFAS exposure. (ref) A total of 88 results was obtained. The geometric means for serum PFHxS, PFOS and PFOA were 13, 11 and 3 ng/mL.

In Ronneby, Sweden, in 2014, i.e. six months after provision of clean water, all residents in the municipality were invited to free-of-charge serum testing. In total 3507 participants were recruited, which was about 13% of the entire Ronneby population at the time.[27] The participation rates from contaminated and minimally contaminated areas were approximately 30% and 5%, respectively. [27] In Ronneby the mains water was the main historical PFAS exposure source. The geometric means for serum PFHxS, PFOS and PFOA were 114, 135 and 6.8 ng/mL for all Ronneby residents.[27] In Ronneby serum was retested to determine if PFAS levels were declining and to determine serum half-lives. [29, 30]

In Australia, between 2016 and 2019, 2392 adults and 195 children were recruited from the PFAS Management Areas in Katherine, Oakey and Williamstown to participate in free-of-charge serum testing. In total, 32% (817/2587) of participants from the exposed communities were current residents of one of the PFAS Management Areas at the time of blood collection. Not all of these participants consumed contaminated borehole water while living in the PFAS Management Areas. The geometric means for serum PFOS, PFHxS and PFOA were 4.9–6.6 ng/mL, 2.9–3.7 ng/mL and 1.3–1.8 ng/mL, respectively. [28] These levels are notably lower than in many of the other studies because the sampling mixed participants who consumed contaminated borehole water with those who did not.

In the United States, The Centers for Disease Control and Prevention (CDC) and the ATSDR conducted free-of-charge serum testing in 10 communities (Westhampton Beach and Quogue Area, New York; Montgomery and Bucks Counties, Pennsylvania; Hampden County, Massachusetts; Berkeley County, West Virginia; New Castle County, Delaware; Spokane County, Washington; Lubbock County, Texas; Fairbanks North Star Borough, Alaska; El Paso County, Colorado and Orange County, New York) that are near current or former military bases and were found to contain PFAS levels in the past exceeding the Environmental Protection Agency's 2016 health advisory of 70 parts per trillion (ppt) for PFOA and PFOS combined. [25] These studies assessed PFAS levels in the serum of some residents in each community living near the current or former military bases where public water systems or private wells had PFAS levels above EPA's health advisories. Participants were selected based on specified criteria with the aim of collecting data that were generalizable to each sampling frame (areas within the site communities where known or expected PFAS exposure occurred). Tap water and indoor dust samples from a subset of participating households were also analyzed. The primary aim was to understand and control exposure rather than to relate exposure to health effect (i.e. epidemiology). Between September 2019 and October 2020, 1988 eligible people (1791 adults and 197 children) from 1094 households participated in the sampling across the 10 locations. The highest age-adjusting geometric means of serum levels across the 10 studies for PFHxS, PFOS and PFOA were 65.6, 39.1 and 8.9 ng/mL. [25]

Also, in the United States, in Pease New Hampshire, a total of 1578 eligible individuals provided serum samples for serum testing in 2015. [26] Many members of this community situated near Pease Airforce Base had consumer water from a contaminated well, which had been contaminated due to historical AFFF use at the base. Eligible participants were those who consumed contaminated drinking water while working on, living on, or attending childcare at the former Air Force base, while it was an active base or in the civilian community of Pease after the base closure. The aim of the study was to understand PFAS exposure. The geometric means for serum PFHxS, PFOS and PFOA were 8.59, 4.12 and 3.09 ng/mL. [26]

In Denmark in 2020, high levels of PFOS and PFHxS were detected in a wastewater treatment plant in Korsør, Denmark, and the source of contamination was found to be a firefighting training facility where AFFF had been regularly used. (ref) In 2021, analyses of the meat from four calves, who had grazed in a field near the firefighting training facility also revealed high levels of PFOS and PFHxS indicative of AFFF contamination. The cattle were the main source of beef intake for members of a local Cow Grazing Association since 1999. Analysis of PFAS in the serum of the Cow Grazing Association (187 individuals) showed particularly high levels of PFOS (mean 43 ng/ml), which is more bioaccumulative in cows than PFHxS and PFOA. (ref) A randomized clinical trial was performed on the exposed population to determine if treatment reduced PFOS serum levels. Despite the treatment effectively decreasing PFOS serum levels in the clinical trial, the Danish authorities decided to not make the treatment generally available. This decision was because they could not conclude that treating individuals to lower PFOS serum levels would provide any health benefits. An exception was made for highly exposed women, who planned a pregnancy. They also decided not to provide retesting to the exposed population as the PFAS levels tested cannot be used to inform on health effects on an individual basis. (ref)

In summary, only the Swedish and Australian studies aimed to relate PFAS serum levels to health effects (as summarized in Report 2). While health data are available for Jersey, this study has too low a number of participants to be used for epidemiological studies. The primary aim of the US studies was to better understand exposure so that it could be effectively reduced going forward.[25] Only

the Swedish study has to date retested a subset of the original participants. The purpose of this retesting was to determine if exposure in the population had declined. [29, 30]

1.3. Testing and retesting in the general population

Exposure to PFAS has been estimated from the concentrations of the target PFAS in serum, plasma, or whole blood in numerous studies conducted around the world since the early 2000s (see multiple references Kato et al.[4]). Observed PFAS serum concentrations vary by geographical location, PFAS type, sex, and age. [1]

NHANES is the most extensive and well-known national serum testing programme and has measured PFAS-levels in blood in the U.S. population since 1999.[31] NHANES PFAS data have been publicly released in 2-year cycles. NHANES is principally designed to assess the health and nutritional status of U.S. adults and children. The survey is unique in that it combines interviews, physical examinations, and analysis of biological samples for contaminants, including PFAS for Americans of 12 years of age and older. The NHANES survey examines a nationally representative sample of about 5,000 persons each year. However, NHANES included a subset of around 2,000 individuals in each cycle for PFAS measurements. In studies such as NHANES that aim is to get a representation sample of the general population the following considerations are required; stratifying your target population by relevant demographics like age, sex, socioeconomic status, region, etc., to capture population diversity; having a sample size that provides sufficient statistical power; and using a random sampling method to avoid selection bias.

Even if NHANES is considered a good representation of the PFAS exposure in the U.S. general population, Wisconsin have initiated their own state-wide survey (The Survey of the Health of Wisconsin (SHOW)) which using similar methodology to NHANES.[32] The aim is to characterize the variability of PFAS exposure in a statewide representative cohort in the US. It can also be used to identify high risk populations and inform state public health standards and interventions, especially among those not living near known contamination sites.

For the majority of the generally-exposed populations examined around the world, the four most commonly studied PFAS have been PFOS, PFOA, PFHxS and PFNA). PFOS usually has the highest serum concentrations followed by PFOA, while other PFAS are detected both at lower concentrations and frequencies. [4] In hot spot contamination areas and occupational settings, the concentration patterns observed often differ from those reported among the general population (e.g. PFHxS is higher than PFOA in serum in an AFFF-impacted population). Interestingly, the ranges of blood concentrations of PFOS, PFOA, PFHxS, and PFNA in the general population are remarkably similar worldwide among many countries, suggesting a common historical exposure source. Higher concentrations of PFOS, PFOA, and PFHxS are found in males compared to females and this has been mainly attributed to monthly blood loss from menstruation in women.

In many of the studies reviewed in the above sections of the report, the contaminated population was often compared to a nearby reference population which in turn was compared to a well-known testing programme for the general population (often NHANES is used). The aim of this comparison exercise is to confirm that the contaminated population is in an isolated region only.

Temporal trend studies of PFOS, PFOA and PFHxS have been undertaken in several countries through retesting a representative sample of the general population at regular intervals.[1, 4] The temporal trend studies are typically “cross-sectional” in design whereby a similar representative cross-section of the population is sampled at each time point (as in NHANES) [31] rather than retesting the same individuals (known as a longitudinal testing design). In NHANES a cross-section of

the US population is sampled every two years since 1999 and the serum analyzed for PFAS. Similar temporal trends have been observed between studies and countries despite some differences in sampling design among studies, pools vs individual specimens, plasma vs serum, sample size, time period and potential regional differences in exposure.[4] The concentrations of these PFAS in blood followed similar increasing trends from the 1970s to the mid-1990s due to the increasing production volumes in this period (e.g. PFOS peaked at about 30 ng/L in the US general population at the turn of the millennium) and then have declined since the early 2000s following their industrial phase out by 3M in 2000-2002. [4] China and some other Asian countries are an exception to these otherwise general time trends because these countries increased production of PFOS and PFOA when 3M phased out their industrial production of long-chain perfluoroalkyl chemistries in 2000-2002,[33] and have only recently announced that they too will cease production of some long-chain perfluoroalkyl chemistries. PFAS are still today ubiquitously detected in people around the world in single digit ng/L levels and declining trends in blood may be plateauing off as serum levels approach a steady-state with background environmental exposure intakes.[1]

1.4. Testing and retesting in occupationally exposed populations, especially firefighters

Christensen and Calkins [5] reviewed occupational exposure studies and identified 92 individual studies for PFAS. Most occupational studies reviewed (~60%) evaluated PFAS exposure in fluorochemical production workers or first responders (mostly firefighters). In addition, occupational studies focused on ski wax technicians, fishermen, textile manufacturing, a metal plating workshop, a powder coating shop, a metalworking shop, a plastic production facility, a pesticide packing plant, outdoor clothing (and gear) shops, offices, college lecture halls, school laboratories, computer rooms, primary/secondary classrooms, furniture shops, printing shops, autobody shops, a mechanical shop, an electrotechnical shop, carpet shops, a car selling store, electronic stores, a sports equipment shop, coffee shops, internet cafes, restaurants, libraries, movie theaters, and hotels. [5] The highest serum levels were reported in fluorochemical workers, but, in comparison to reference populations, one or more PFAS were elevated in most workers and in most workplaces that were assessed in the review. [5] Here we provide a summary only of the research done on occupation exposure of PFAS for firefighters as it is most relevant occupational exposure for Jersey.

Serum testing of PFAS in firefighters was reviewed by Rosenfeld et al. [6]. The 10 studies that were reviewed by Rosenfeld et al. in the US and Australia showed that firefighters have elevated serum levels of certain PFAS such as PFOS and PFHxS [5]. In Australia, Rotander et al. [34] studied 149 firefighters working with AFFF at training facilities in Australia's Airservices Aviation Rescue Fire Fighting Service and reported that firefighter PFOS and PFHxS serum levels were 6–10 times and 10–15 times higher, respectively, than in the general population. A larger study followed on 799 current and former Airservices staff, with 130 staff from the earlier study.[35] Although PFAS were still elevated, the geometric mean dropped between 2015 and 2018, suggesting that levels continued to decline since the 2005 phase-out of 3M Lightwater AFFF in Australia. Nilsson et al.[35] further found that PFOS and PFHxS serum levels were positively correlated with length of employment working with AFFF. Firefighters who started work in Australia before 2005 had serum concentrations of PFHxS and PFOS higher than the general population, while those who started working after 2005 had levels similar to the general population. In the US, eight additional studies reported elevated levels of PFAS in the serum of both fulltime and volunteer firefighters.[35]

Dermal and inhalation exposure from PFAS-impregnated turnout gear have both been suggested to be exposure pathways for firefighters, but these pathways are considered of lesser importance compared to exposure from the use of AFFF during training and firefighting.[6] The fact that Australian firefighters who commenced worked after 2005, and still wore PFAS impregnated turnout

gear, had similar levels to the general population provides supporting evidence that AFFF-derived exposure is much more important than exposure related to turnout gear.[35] Modern fluorotelomer-based AFFF is based on short-chain C6 PFAS chemistry. No exposure to PFOS or PFHxS is possible from the use of modern fluorotelomer-based AFFF as it does not contain these substances.[36]

1.5. Discussion on strategies for testing and retesting serum for PFAS

In the 2006 NRCNA book[7] on testing of contaminants in humans, it recommended that it is first necessary to determine the purpose of retesting, which can be several:

- Tracking exposure over time: These studies monitor the levels of PFAS or biomarkers in individuals over extended periods. The aim is primarily to understand how exposure to PFAS changes over time and can be used e.g. to derive serum half-lives.
- Assessing health outcomes: By correlating test data with health outcomes, researchers can identify potential links between exposure to certain chemicals and the development of diseases or health conditions over time.
- Evaluating public health interventions: To assess the effectiveness of public health policies and interventions aimed at reducing exposure to harmful substances. This helps in determining whether these measures are successful and where improvements might be needed.
- Identifying at-risk populations: These studies can highlight specific groups within the population that are more vulnerable to certain exposures, such as children, pregnant women, or occupational groups. This information is crucial for targeted public health strategies.
- Understanding environmental changes: To reveal how changes in environmental levels impact human exposure over time.
- Supporting regulatory decisions: The data from these studies provide evidence that can inform regulatory bodies in setting safety standards and guidelines for exposure to various chemicals.

When it comes to retesting of individuals with elevated PFAS exposures, the following guidance is given in the NRCNA 2022 report,[8] which provides specific guidance on PFAS testing:

- For individual tests, consider confirmatory retesting when the result is much higher or lower than anticipated given exposure history;
- Consider retesting to understand exposure changes due to:
 - public health actions (such as drinking water treatment programs or site cleanup are taken to reduce exposure);
 - patients take actions to reduce exposure (such as installing water filters, moving from a community with known high levels of PFAS in drinking water, or modifying occupational exposures); or
 - the patient moves into a community with known high levels of PFAS or otherwise has a suspected increase in exposure risk.
- If there is interest in follow-up testing of PFAS to determine declines in exposure and determination of serum half-lives, allow at least a year between each retesting.
- Retesting is of no or limited value if initial serum levels are low and exposure does not change.

This guidance given above taken from the NRCNA 2022 report[8] is purely related to retesting for the purpose of understanding exposure. Also, no guidance is given above as to what is considered “low” serum levels. However, it is further recommended in the NRCNA 2022 report[8] that clinicians should use serum or plasma concentrations of the sum of PFAS to inform clinical care of exposed patients, using the following guidelines for interpretation:

- Adverse health effects related to PFAS exposure are not expected at less than 2 ng/mL.
- There is a potential for adverse effects, especially in sensitive populations, between 2 and 20 ng/mL.
- There is an increased risk of adverse effects above 20 ng/mL.

Therefore “low” serum levels can be concluded to be less than 2 ng/L. However, the above advice may lead some individuals to believe that if they have serum levels above 2 ng/L they are at a higher risk of certain health effects related to PFAS exposure. However, it is impossible to predict health outcomes for *individuals* based on their PFAS serum levels. The authors presumably mean that there is a potential increased risk of adverse effects *on the population level* at exposure levels above 20 ng/L. It is nevertheless precautionary guidance because everyone in an industrialized country had levels of at least 20 ng/L 20 years ago and levels of 2 ng/L are fairly typical for the general population at the time of writing in 2024.

In practice, retesting for clinical management purposes in contaminated communities has not been undertaken often and is not recommended by some health authorities. For example, in Denmark retesting is not recommended in contaminated communities for the following reasons (ref):

- PFAS-levels cannot be used to predict health outcomes;
- Testing of blood samples need to be actionable, i.e. guide medical decisions and treatments;
- Counseling for highly exposed individuals does not differ from that of the background population.

At Ronneby in Sweden, the authorities follow the same general approach as in Denmark and do not offer retesting of serum levels to those individuals who took part in the initial broad testing of PFAS in the contaminated community. (ref) They also do not offer testing, or recommend individuals to test themselves, for PFAS serum levels if they live in the contaminated area but have previously been tested. Similar to in Denmark, they argue that there are no medical reasons for testing serum levels of PFAS because the test result cannot be used to predict anything about the individual's health or risk of future illness. (ref) In Ronneby, there is, however, serum retesting ongoing within various research projects focused on understanding serum half-lives of PFAS,[29, 30] but there is no clinical management connected to this retesting.

In the cases where retesting in contaminated communities has been done, reviewed above, it is clear that retesting was done largely for understanding changes of exposure, e.g. in order to improve understanding of the half life of PFAS moieties in the community, or for other research purposes, rather than to monitor the patient's wellbeing (i.e. clinical management). It can also be concluded that Jersey is unique in only testing PFAS in the serum of individuals with symptoms consistent with conditions that have been associated with PFAS exposure. All other studies tested individuals asymptotically in the first testing timepoint and then typically retested a subsample of the original population at a later timepoint to determine if exposure had declined. Health data are usually collected from the sampled population for epidemiological research, and rarely for clinical management purposed. A few research studies have resampled PFAS levels in order to ascertain if there is a relationship with the course of a particular illness or biomarker related to PFAS

exposure,[37-39] and other studies have retested in order to assess suitability to enter or to remain in programmes of clinical intervention seeking to lower PFAS body burden.[40, 41] In one identified case, regular retesting of serum was performed in conjunction with regular health monitoring, but this was connected to a class action lawsuit and the motivation for retesting is very different compared to other contaminated communities managed by local health authorities. There is limited guidance provided for when retesting should be ceased, although in the NRCNA 2022 report it is suggested that adverse health effects related to PFAS exposure are not expected at serum levels less than 2 ng/mL. [8] If one accepts the conclusion regarding lack of adverse health effects below this level, it would be unnecessary to retest individuals once serum levels were below 2 ng/mL.

References

1. Sunderland, E.M., et al., *A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects*. Journal of Exposure Science & Environmental Epidemiology, 2019. **29**(2): p. 131-147.
2. Carignan, C.C., et al., *Self-Collection Blood Test for PFASs: Comparing Volumetric Microsamplers with a Traditional Serum Approach*. Environmental Science & Technology, 2023. **57**(21): p. 7950-7957.
3. Olsen, G.W., *PFAS Biomonitoring in Higher Exposed Populations*, in *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*, J.C. DeWitt, Editor. 2015, Springer International Publishing: Cham. p. 77-125.
4. Kato, K., X. Ye, and A.M. Calafat, *PFASs in the General Population*, in *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*, J.C. DeWitt, Editor. 2015, Springer International Publishing: Cham. p. 51-76.
5. Christensen, B.T. and M.M. Calkins, *Occupational exposure to per- and polyfluoroalkyl substances: a scope review of the literature from 1980-2021*. J Expo Sci Environ Epidemiol, 2023. **33**(5): p. 673-686.
6. Rosenfeld, P.E., et al., *Perfluoroalkyl substances exposure in firefighters: Sources and implications*. Environmental Research, 2023. **220**: p. 115164.
7. Council, N.R., *Human Biomonitoring for Environmental Chemicals*. 2006, Washington, DC: The National Academies Press. 316.
8. National Academies of Sciences, E., and Medicine; Health and Medicine Division; Division on Earth and Life Studies; Board on Population Health and Public Health Practice; Board on Environmental Studies and Toxicology; Committee on the Guidance on PFAS Testing and Health Outcomes. *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up*. Washington (DC): National Academies Press (US); 2022 Jul 28. 1, Introduction. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK584707/>.
9. Lindstrom, A.B., et al., *Application of WWTP Biosolids and Resulting Perfluorinated Compound Contamination of Surface and Well Water in Decatur, Alabama, USA*. Environmental Science & Technology, 2011. **45**(19): p. 8015-8021.
10. Agency for Toxic Substances and Disease Registry (ATSDR) (2013) *HEALTH CONSULTATION: Exposure Investigation Report Perfluorochemical Serum Sampling In the vicinity of Decatur, Alabama Morgan, Lawrence, and Limestone Counties*. Available at: https://www.atsdr.cdc.gov/HAC/pha/Decatur/Perfluorochemical_Serum%20Sampling.pdf. Accessed: 29/10/2014.
11. Worley, R.R., et al., *Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community*. Environ Int, 2017. **106**: p. 135-143.
12. Emmett, E.A., et al., *Community exposure to perfluorooctanoate: Relationships between serum concentrations and exposure sources*. Journal of Occupational and Environmental Medicine, 2006. **48**(8): p. 759-770.

13. Frisbee, S.J., et al., *The C8 health project: design, methods, and participants*. Environ Health Perspect, 2009. **117**(12): p. 1873-82.
14. Bartell, S.M., et al., *Rate of Decline in Serum PFOA Concentrations after Granular Activated Carbon Filtration at Two Public Water Systems in Ohio and West Virginia*. Environmental Health Perspectives, 2010. **118**(2): p. 222-228.
15. Steenland, K., et al., *Review: Evolution of evidence on PFOA and health following the assessments of the C8 Science Panel*. Environment International, 2020. **145**: p. 106125.
16. Kotlarz, N., et al., *Measurement of Novel, Drinking Water-Associated PFAS in Blood from Adults and Children in Wilmington, North Carolina*. Environmental Health Perspectives. **128**(7): p. 077005.
17. Kotlarz, N., et al., *Reanalysis of PFO5DoA Levels in Blood from Wilmington, North Carolina, Residents, 2017–2018*. Environmental Health Perspectives. **132**(2): p. 027701.
18. Hölzer, J., et al., *Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water*. Environ Health Perspect, 2008. **116**(5): p. 651-7.
19. Hölzer, J., et al., *One-year follow-up of perfluorinated compounds in plasma of German residents from Arnsberg formerly exposed to PFOA-contaminated drinking water*. Int J Hyg Environ Health, 2009. **212**(5): p. 499-504.
20. Brede, E., et al., *Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany*. Int J Hyg Environ Health, 2010. **213**(3): p. 217-23.
21. Zhou, Z., et al., *Highly Elevated Serum Concentrations of Perfluoroalkyl Substances in Fishery Employees from Tangxun Lake, China*. Environmental Science & Technology, 2014. **48**(7): p. 3864-3874.
22. Ingelido, A.M., et al., *Biomonitoring of perfluorinated compounds in adults exposed to contaminated drinking water in the Veneto Region, Italy*. Environ Int, 2018. **110**: p. 149-159.
23. Pitter, G., et al., *Serum Levels of Perfluoroalkyl Substances (PFAS) in Adolescents and Young Adults Exposed to Contaminated Drinking Water in the Veneto Region, Italy: A Cross-Sectional Study Based on a Health Surveillance Program*. Environmental Health Perspectives. **128**(2): p. 027007.
24. Canova, C., et al., *PFAS exposures in Veneto, Italy: the role of biomonitoring in addressing a serious public health threat*. ISEE Conference Abstracts. **2022**(1).
25. ATSDR, *PFAS Exposure Assessments Final Report: Findings Across Ten Exposure Assessment (EA) Sites*. <https://www.atsdr.cdc.gov/pfas/activities/assessments/final-report.html>. Accessed: 29/10/2024. 2022.
26. Daly, E.R., et al., *Per- and polyfluoroalkyl substance (PFAS) exposure assessment in a community exposed to contaminated drinking water, New Hampshire, 2015*. Int J Hyg Environ Health, 2018. **221**(3): p. 569-577.
27. Xu, Y., et al., *Serum perfluoroalkyl substances in residents following long-term drinking water contamination from firefighting foam in Ronneby, Sweden*. Environment International, 2021. **147**: p. 106333.
28. Smurthwaite K, Lazarevic N, Bräunig J, Mueller J, Nilsson S, D'Este C, Lucas R, Armstrong A, Lal A, Trevenar S, Law HD, Gad I, Hosking R, Joshy A, Clements A, Lane J, Batterham P, Banwell C, Miller A, Randall D, Korda R, Kirk M. *PFAS Health Study Component two: Blood serum study of PFAS exposure, related risk factors and biochemical markers of health*. Canberra (AU): The Australian National University; 2021 Dec.
29. Li, Y., et al., *Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water*. Occupational and Environmental Medicine, 2018. **75**(1): p. 46-51.
30. Xu, Y., et al., *Serum Half-Lives for Short- and Long-Chain Perfluoroalkyl Acids after Ceasing Exposure from Drinking Water Contaminated by Firefighting Foam*. Environmental Health Perspectives. **128**(7): p. 077004.

31. Calafat, A.M., et al., *Serum Concentrations of 11 Polyfluoroalkyl Compounds in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000*. Environmental Science & Technology, 2007. **41**(7): p. 2237-2242.
32. Pomazal, R., et al., *Determinants of per- and polyfluoroalkyl substances (PFAS) exposure among Wisconsin residents*. Environmental Research, 2024. **254**: p. 119131.
33. Wang, T., et al., *Levels, Isomer Profiles, and Estimated Riverine Mass Discharges of Perfluoroalkyl Acids and Fluorinated Alternatives at the Mouths of Chinese Rivers*. Environmental Science & Technology, 2016. **50**(21): p. 11584-11592.
34. Rotander, A., et al., *Elevated levels of PFOS and PFHxS in firefighters exposed to aqueous film forming foam (AFFF)*. Environ Int, 2015. **82**: p. 28-34.
35. Nilsson, S., et al., *Serum concentration trends and apparent half-lives of per- and polyfluoroalkyl substances (PFAS) in Australian firefighters*. Int J Hyg Environ Health, 2022. **246**: p. 114040.
36. Barzen-Hanson, K.A., et al., *Discovery of 40 Classes of Per- and Polyfluoroalkyl Substances in Historical Aqueous Film-Forming Foams (AFFFs) and AFFF-Impacted Groundwater*. Environmental Science & Technology, 2017. **51**(4): p. 2047-2057.
37. Fitz-Simon, N., et al., *Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid*. Epidemiology, 2013. **24**(4): p. 569-76.
38. Lin, P.D., et al., *Per- and polyfluoroalkyl substances and blood lipid levels in pre-diabetic adults-longitudinal analysis of the diabetes prevention program outcomes study*. Environ Int, 2019. **129**: p. 343-353.
39. Steenland, K., et al., *Ulcerative Colitis and Perfluorooctanoic Acid (PFOA) in a Highly Exposed Population of Community Residents and Workers in the Mid-Ohio Valley*. Environmental Health Perspectives, 2013. **121**(8): p. 900-905.
40. Møller, J.J., et al., *Substantial decrease of PFAS with anion exchange resin treatment – A clinical cross-over trial*. Environment International, 2024. **185**: p. 108497.
41. Gasiorowski, R., et al., *Effect of Plasma and Blood Donations on Levels of Perfluoroalkyl and Polyfluoroalkyl Substances in Firefighters in Australia: A Randomized Clinical Trial*. JAMA Netw Open, 2022. **5**(4): p. e226257.

The wider risks and benefits of plasma removal

Safety Measures in Plasma Donation

To ensure donor safety, in altruistic plasma donation, stringent screening processes are in place. Potential donors undergo comprehensive health assessments, including medical history reviews, physical examinations, and laboratory testing. Eligibility criteria often include age restrictions (usually 18 to 65 years), weight requirements (typically over 50 kg or 110 lbs), and overall good health (JPAC, 2024). The use of sterile, single-use collection kits minimizes the risk of infection and cross-contamination. Apheresis machines are designed with closed systems where the blood contacts only sterile, disposable components (JPAC, 2024). Qualified healthcare professionals conduct the donation process, continuously monitoring donors for any adverse reactions. Vital signs such as blood pressure, pulse, and haemoglobin levels are checked before, during, and after the procedure (JPAC, 2024).

Regulatory bodies like the UK Medicines and Healthcare Products Regulatory Agency (MHRA), U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) enforce strict guidelines for plasma collection centres. Compliance with Good Manufacturing Practices (GMP) and regular inspections are necessary to ensure high safety standards (EQDM, 2023).

Common Side Effects

Most plasma donations proceed without significant issues. However, some donors may experience mild, transient side effects:

- **Bruising or Discomfort at the Needle Site:** Minor bruising, bleeding, or pain can occur at the venipuncture site (Crocco & D'Elia, 2007).
- **Fatigue or Dizziness:** Temporary feelings of tiredness or light-headedness may result from fluid removal but typically resolve quickly (Crocco & D'Elia, 2007).
- **Hypocalcaemia Symptoms:** Tingling sensations in the lips or fingers due to citrate anticoagulant binding calcium, leading to temporary hypocalcaemia (Winters et al., 2011).

Rare but Serious Complications

While serious adverse events are rare, they can occur:

- **Vasovagal Reactions:** A reflex resulting in sudden fainting due to a drop in heart rate and blood pressure. Occurs in approximately 1% of donations (Philip et al., 2014).
- **Citrate Reaction:** An adverse response to citrate anticoagulant used during plasmapheresis, leading to symptoms like muscle cramps, nausea, or arrhythmias in severe cases. Rarely happens, with most reactions being mild (Winters et al., 2011).
- **Allergic Reactions:** Hypersensitivity to materials used during donation, such as the anticoagulant or equipment components. These are extremely rare but can be life-threatening (Crocco et al., 2009).

Long-Term Safety Considerations

Protein Levels: Frequent plasma donation could potentially lower plasma protein levels. This can potentially be hazardous to health (D'Aes et al., 2024)

Iron Levels Unlike whole blood donation, plasma donation has minimal impact on iron stores because red blood cells are returned to the donor (Simon, 2002).

Immunoglobulin Levels Slight decreases in immunoglobulin G (IgG) levels have been observed. This could potentially affect the ability to fight infections, although the reduction is usually small (D'Aes et al., 2024).

Conclusion

Plasma donation is a generally safe and well-tolerated procedure. While minor side effects are relatively common, serious complications are rare and manageable with proper protocols. Rigorous screening, adherence to regulatory standards, and continuous monitoring contribute to donor safety.

Capital and revenue requirements for establishing and running a plasma donation service

Necessary Equipment

- **Apheresis Machines:** These devices that separate plasma from whole blood through centrifugation or filtration. They must be MHRA-approved and capable of performing plasmapheresis efficiently and safely.
- **Sterile Disposable Kits:** Needles, tubing, collection bags, and anticoagulant solutions. Single-use kits prevent cross-contamination and ensure sterility.
- **Medical Examination Equipment:** Blood pressure monitors, haemoglobin testing devices, scales, and temperature gauges. These are used to assess donor eligibility and monitor vital signs pre- and post-donation.
- **Emergency Equipment:** Automated External Defibrillators (AEDs), oxygen tanks, and first aid kits. To address any adverse reactions or medical emergencies promptly.

Required Personnel

- **Lead clinician:** Probably a medical consultant with expertise in transfusion medicine or haematology. Role includes oversight of medical procedures, donor eligibility criteria, and compliance with medical standards (JPAC, 2024).
- **Specialist nurses:** To perform vein punctures, operate apheresis machines, and monitor donors during the procedure. They need to be certified in phlebotomy and trained in the use of specific apheresis equipment.
- **Maintenance and Cleaning Personnel:** To ensure cleanliness of the facility and proper functioning of equipment. This is critical for infection control and meeting health standards.

Maintenance and Regulatory Compliance

- **Regular Servicing of Equipment:** Apheresis machines and refrigeration units require routine checks and servicing by qualified technicians.
- **Calibration of Equipment:** Medical devices must be calibrated regularly to ensure accuracy^(ISO, 2022).
- **Facility Cleaning Protocols:** Adherence to strict cleaning schedules for donor areas, equipment, and common spaces.

- **Infection Control:** Implementation of standard precautions to prevent cross-contamination
- **Licensing and Accreditation:** Obtain necessary licenses from health regulatory organisations.
- **Standard Operating Procedures (SOPs):** Develop and maintain SOPs for all processes, aligning with MHRA, FDA and European Medicines Agency (EMA) guidelines.
- **Staff Training and Certification:** Ongoing education to keep staff updated on best practices and regulatory changes.
- **Audits and Inspections:** Regular internal audits and readiness for external inspections.
- **Documentation:** Comprehensive record-keeping for traceability and accountability (EQDM, 2023).

Offering a plasma donation service involves more than just collecting plasma; it requires a robust infrastructure of specialised equipment, skilled personnel, and stringent maintenance protocols.

Cost of an Apheresis Machine for Human Use

Capital cost per machine

The cost of an apheresis machine for human use in the United Kingdom can vary significantly based on several factors, including the manufacturer, model, features, whether the machine is new or refurbished, and the supplier. The approximate price range for a new apheresis machine is between £20,000 and £50,000 per unit.

Additional Costs to Consider

- **Maintenance and Service Contracts:** Essential for the safe and effective operation of the machine, there will be regular maintenance and calibration, carried out by facility staff. In addition to that there would be a requirement for a service contract with the manufacturer. These can be of the order of £5,000 per annum.
- **Consumables:** Each plasma collection procedure requires a single-use kit, costing between £30 and £50 each. In addition to this, there would need to be anticoagulants and other solutions that are used in the plasmapheresis process.
- **Training and Staffing:** In addition, the salary costs of the staff described above, staff must be trained to operate the machine safely. Some manufacturers offer training programs, which may be included or charged separately.
- **Regulatory Compliance:** Compliance with the Medicines and Healthcare products Regulatory Agency (MHRA) regulations may involve fees and/or modifications to the facility.

In summary

Bringing all of this together, it is a reasonable assumption that the capital outlay for a service would be at least £100,000 and the revenue costs, assuming 500 plasma removal activities (10 interventions each for 50 people) in year 1 and half time consultant cover and full time cover from other staff would be between £150,000 and £200,000 per annum.

- Crocco, A., & D'Elia, D. (2007). Adverse reactions during voluntary donation of blood and/or blood components. A statistical-epidemiological study. *Blood Transfus*, 5(3), 143-152. <https://doi.org/10.2450/2007.0005-07>
- Crocco, I., Franchini, M., Garozzo, G., Gandini, A. R., Gandini, G., Bonomo, P., & Aprili, G. (2009). Adverse reactions in blood and apheresis donors: experience from two Italian transfusion centres. *Blood Transfus*, 7(1), 35-38. <https://doi.org/10.2450/2008.0018-08>
- D'Aes, T., van den Hurk, K., Schroyens, N., Mikkelsen, S., Severijns, P., De Buck, E., O'Leary, P., Tiberghien, P., Compennolle, V., Erikstrup, C., & Van Remoortel, H. (2024). Balancing Donor Health and Plasma Collection: A Systematic Review of the Impact of Plasmapheresis Frequency. *Transfusion Medicine Reviews*, 150851. <https://doi.org/https://doi.org/10.1016/j.tmr.2024.150851>
- EQDM. (2023). *Guide to the preparation, use and quality assurance of blood components*. European Directorate for the Quality of Medicines and Healthcare. Retrieved 29 Oct from <https://www.edqm.eu/en/blood-guide>
- ISO. (2022). ISO 15189:2022 Medical laboratories — Requirements for quality and competence. In: International Organization for Standardization.
- JPAC. (2024, 24/10/2024). *Guidelines for the Blood Transfusion Services in the UK*. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Retrieved 29 October from <https://www.transfusionguidelines.org/red-book>
- Philip, J., Sarkar, R. S., & Jain, N. (2014). A single-centre study of vasovagal reaction in blood donors: Influence of age, sex, donation status, weight, total blood volume and volume of blood collected. *Asian J Transfus Sci*, 8(1), 43-46. <https://doi.org/10.4103/0973-6247.126690>
- Simon, T. L. (2002). Iron, iron everywhere but not enough to donate. *Transfusion*, 42(6), 664. <https://doi.org/10.1046/j.1537-2995.2002.00121.x>
- Winters, J., Crookston, K., Eder, A., King, K., Kiss, J. E., Sarode, R., & Szczepiorkowski, Z. (2011). *Therapeutic Apheresis. A Physician's Handbook*.

Types of plasma removal treatment

Plasma, the liquid component of blood, plays a crucial role in transporting nutrients, hormones, and proteins throughout the body. It constitutes about 55% of total blood volume and contains essential components such as clotting factors, immunoglobulins, and albumin. Medical procedures involving plasma—such as plasma donation, plasmapheresis, and plasma exchange—are vital for both therapeutic and donation purposes. While these terms are sometimes used interchangeably, they refer to distinct processes with specific applications. This essay explores the differences between plasma donation, plasmapheresis, and plasma exchange, highlighting their procedures, purposes, and clinical significance.

Plasma Donation

Plasma donation is a process where a healthy person altruistically donates plasma for medical use. The collected plasma is primarily used for manufacturing plasma-derived medicinal products (PDMPs), such as clotting factors for haemophilia patients, immunoglobulins for immune deficiencies, and albumin for critical care situations.

During plasma donation, blood is taken from the donor and passed through a machine that separates, using centrifugation or filtration, plasma from other blood components. The red blood cells, white blood cells, and platelets are then returned to the donor's bloodstream, while the plasma is collected for use. This process typically takes about 1 to 2 hours and can be performed more frequently than whole blood donation because the body replenishes plasma faster than red blood cells (JPAC, 2024).

Plasmapheresis

Plasmapheresis is a medical procedure that involves the removal, treatment, and return of plasma to the patient's body. It is a form of apheresis specifically targeting plasma components. Plasmapheresis can be therapeutic or altruistic. In therapeutic plasmapheresis, harmful substances in the plasma are removed to treat certain medical conditions (Schwartz et al., 2016).

In plasmapheresis, blood is taken from the patient and passed through an apheresis machine. The plasma is separated from the cellular components. Depending on the treatment goal, the plasma may be treated to remove specific substances (like antibodies or toxins) and then returned to the patient along with the blood cells (Kaplan, 2013). The procedure usually takes 1 to 3 hours and may require multiple sessions depending on the condition being treated (Mokrzycki & Kaplan, 1994).

Plasma Exchange (Therapeutic Plasma Exchange)

Plasma exchange, also known as therapeutic plasma exchange (TPE), is a procedure where a patient's plasma is removed and replaced with a substitute, such as donor plasma or albumin solutions. The primary goal is to eliminate pathogenic substances present in the plasma that contribute to disease processes (Winters, 2012).

Similar to plasmapheresis, blood is withdrawn from the patient and separated into plasma and cellular components. However, in plasma exchange, the patient's plasma is discarded entirely, and the blood cells are combined with replacement fluid before being returned to the patient.

(Cervantes et al., 2023). The replacement fluids can be fresh frozen plasma, albumin, or crystalloid solutions, depending on the clinical scenario.

Comparative Analysis

- **Plasma Donation:** Intended for collecting plasma from healthy donors to produce PDMPs for patients in need. Donor's plasma is collected, and blood cells are returned; used for manufacturing medical products.
- **Plasmapheresis:** Used therapeutically to remove specific components from a patient's plasma and return the treated plasma. Patient's plasma is treated and returned; focuses on filtering out specific pathogenic components.
- **Plasma Exchange:** Involves the removal and replacement of a patient's plasma to eliminate harmful substances. Patient's plasma is entirely replaced with substitute fluids; removes a broader range of substances.

Different studies have looked at different approaches to plasma removal in PFAS exposed people. They have been considered together in this report.

Cervantes, C. E., Bloch, E. M., & Sperati, C. J. (2023). Therapeutic Plasma Exchange: Core Curriculum 2023. *American Journal of Kidney Diseases*, 81(4), 475-492.
<https://doi.org/10.1053/j.ajkd.2022.10.017>

JPAC. (2024, 24/10/2024). *Guidelines for the Blood Transfusion Services in the UK*. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Retrieved 29 October from <https://www.transfusionguidelines.org/red-book>

Kaplan, A. A. (2013). Therapeutic plasma exchange: a technical and operational review. *J Clin Apher*, 28(1), 3-10. <https://doi.org/10.1002/jca.21257>

Mokrzycki, M. H., & Kaplan, A. A. (1994). Therapeutic plasma exchange: complications and management. *Am J Kidney Dis*, 23(6), 817-827. [https://doi.org/10.1016/s0272-6386\(12\)80135-1](https://doi.org/10.1016/s0272-6386(12)80135-1)

Schwartz, J., Padmanabhan, A., Aqui, N., Balogun, R. A., Connelly-Smith, L., Delaney, M., Dunbar, N. M., Witt, V., Wu, Y., & Shaz, B. H. (2016). Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *J Clin Apher*, 31(3), 149-162. <https://doi.org/10.1002/jca.21470>

Winters, J. L. (2012). Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. *Hematology Am Soc Hematol Educ Program*, 2012, 7-12. <https://doi.org/10.1182/asheducation-2012.1.7>