Point-of-care device for rapid measurement of plasma fibrinogen in whole blood

Commercial Case Feasibility Study – Final Report

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1. Introduction

Fibrinogen level is one of the most important predictors of haemorrhage during surgery. Similarly, pre-delivery fibrinogen level is an important predictor of postpartum haemorrhage (PPH) which is one of the leading causes of maternal mortality and morbidity during childbirth. Fibrinogen level also falls sharply when a (trauma) patient is bleeding internally.

Fibrinogen level monitoring (followed by Fibrinogen replacement therapy where necessary) therefore reduces the risks of severe haemorrhage and is critical to patient health.

Dr Vitaly Efremov and his colleagues at Dublin City University have successfully demonstrated a portable point-of-care (POC) device that provides rapid measurement of plasma fibrinogen (FG) concentration directly in a 40ul sample of whole blood (WB). This product has been developed to have advantages over the existing approaches to FG level monitoring:

- It provides a faster result than the von Clauss assay, which is a (cumbersome) laboratory test with a turnaround time of 30 minutes
- It is more accurate than the TEG Functional Fibrinogen Assay (TEG FF), and also better suited to use at point of care than the TEG and ROTEM devices (e.g. TEG weighs 5kg and required connection to a PC and adjacent wet chemistry space).

The DCU team believe that their device better satisfies the need for a compact and simple assay that provides a rapid result - and that can be performed in the delivery room or operating theatre. Viadynamics has been retained to interview Key Opinion Leaders (KOLs), perform a commercial case analysis, and gather the information necessary for the future development of a business plan.

The Viadynamics team of Nicholas Duggan (Viadynamics) and Patrick Hall (Designing Science) have extensive experience supporting the commercialisation of high potential technologies emerging from Irish and UK universities. This includes performing feasibility study assignments across a wide range of medical technology opportunities, product design & development of medical devices, and supporting & driving the formation of new med-tech businesses.

This document is our report.

2. Executive Summary

Dr Vitaly Efremov and his colleagues at Dublin City University have successfully demonstrated F-Point, a portable point-of-care device that provides rapid measurement of plasma fibrinogen concentration directly in a 40ul sample of whole blood.

The Viadynamics team interviewed Key Opinion Leading (KOL) clinicians and clinical researchers across obstetrics and trauma surgery to validate the clinical need for F-Point. In obstetrics, we found that clinicians are eager to have such a device available to them when dealing with cases of postpartum haemorrhage. There are 90,000 cases across the EU and US per annum, and using F-Point three times on average during each case of postpartum haemorrhage would mean use of 270,000 tests per annum.

Emergency room clinicians would use F-Point when dealing with patients who might be suffering from (difficult to diagnose) internal bleeding – victims of gun & knife crime, and people who have sustained serious injury in road accidents or fallen from a height. This usage would potentially add another 1.16m tests per annum (EU and US). There is also a related opportunity, to supply F-Point to the military for use in triaging of battlefield casualties.

To succeed as a point of care test, F-Point will have to be 'accurate enough', provide a result in a small number of minutes, be easy to use, and robust to operation outside of the laboratory. The incumbent tests for Fibrinogen (the von Clauss assay and TEG/ROTEM devices) are not designed for or used at point of care. Consequently, F-Point has a strong USP at present. However, there is a risk that another device will emerge, optimised for point of care, and become a serious competitor.

A programme of work has been defined to develop a clinic-ready version of F-Point and work with Key Opinion Leader clinicians and clinical researchers to both validate the device and prepare the ground for a successful market launch. Costed at commercial rates, this work would need approximately €1.5m in funding. Throughout this work, a number of technical and design choices will have to be made; that optimise the performance and usability of the device at point of care while minimising the regulatory classification and regulatory burden of the device.

F-Point will generate sales from both the device, and a consumable. The total market opportunity for consumables is valued at €14.3m per annum. The supply of devices to the 13,400 hospital departments where F-Point might be used can grow to €8m per annum at maturity. The total market opportunity is therefore €22.3m per annum.

Factoring in the need to educate clinicians and roll-out the launch of F-Point across obstetrics to trauma applications, projected revenues are forecast to grow to €12.9m by 'Year 5' after launch.

The Viadynamics team have used a sales price of €10 per consumable in these calculations. Previous analysis by Reimbursement Strategies LLC for the F-Point team identified a likely reimbursement amount of $14.02 in the US, while the F-Point team predict a manufacturing cost of less than €2 per test. A sales price of €3,000 per device has been used in our financial modelling. The device will cost below €1,000 to manufacture.

F-Point resolves an un-met clinical need, clinicians are eager to use a point of care test for Fibrinogen and a significant market opportunity exists. The Viadynamics team recommends that the F-Point team continue to develop the device at DCU and work towards placing the device into a start-up company. A license to, or marketing agreement with, an existing supplier of in vitro diagnostics could be explored later, in order to maximise the ability to reach 100% of the market.

3. KOL report

The Viadynamics team interviewed a number of Key Opinion Leading (KOL) researchers and industry experts. These people are listed in the table below.

Table 1; people interviewed

KOL	Organisation
Dr. Patrick (Patch) Thornton	Rotunda Hospital, Dublin
Dr. Roger McMorrow	Clinical Director & Consultant Anaesthetist National Maternity Hospital, Dublin
Prof. Fionnuala Ní Áinle	Consultant Haematologist, Mater Misericordiae University Hospital and Rotunda Hospital, Dublin
Professor Beverley Hunt	Director of the Haemostasis Research Unit, Guy's and St. Thomas's Hospital Trust, UK
Dr. Nicola Mutch	Institute of Medical Sciences Aberdeen University
Dr Win Sen Kuan Dr Kanwar Sudhir Lather	Emergency Medicine Department National University Hospital, Singapore
Prof Charmaine Childs	Professor of Clinical Science Sheffield Hallam University
Oliver Tang	GP and medical technology expert Shanghai, China
Dr Brendan McGrath	Senior Lecturer University of Manchester.
Dr Kyle Stewart	Torbay and South Devon NHS Foundation Trust

Key insights from these conversations are set out below. Notes of the individual conversations with the KOLs listed in the table above are set out in Appendix 1.

Clinical need in obstetrics is validated:

- Clinicians are currently playing 'trial and error' when prescribing Fibrinogen for postpartum haemorrhage patients, and then using a lab test for subsequent confirmation, and to provide a record to what happened during the bleeding event
- Clinicians are keen to see a point of care test for Fibrinogen available to them, to enable them to more easily arrive at the optimum prescription.

Clinical need in trauma is also validated:

- Internal bleeds are difficult to diagnose, and a point of care test for Fibrinogen would determine this
- The test is relevant to gun & knife injuries, and also people seriously injured in road traffic accidents
- It would be used in the Emergency Department, and every ED might have one
- An Emergency Department might conduct 1-3 test per week (100 per annum)
- The test would also potentially be used by first responders, and by the military (when dealing with battlefield injuries).

F-Point will do a different job to the von Clauss assay:

- The von Clauss assay is a laboratory test, and its use is 'pre-planned'
- It is the current standard for Fibrinogen testing, and is expected to give an accurate reading
- In contrast, F-Point should be quick and easy enough for use at 'point of care', but does not have to be as accurate.

Does a different job to TEG/ROTEM:

- ROTEM is designed to provide a wide range of information (on many parameters)
- Its use during a surgery is pre-planned – to provide the information that the surgical team need, at the time when they expect to need it
- It is not designed to provide a rapid result in an emergency situation
- And the device is not robust enough for use at point of care.

The use case for F-Point is clear to clinicians:

- Administer clotting agents once a major bleed occurs
- These include Fibrinogen (clotting agent) plus Tranexamic acid (TXA) to prevent clots from breaking down (antifibrinolytic)
- Test Fibrinogen level using a point of care device
- Use reading from this device to identify whether to administer additional Fibrinogen or not
- Repeat test at intervals until bleeding is brought under control. Continue to add Fibrinogen as required (a clinician can administer up to 12g to an individual patient)
- The clinician will continue to send bloods to lab as before, throughout the surgery, to build a record of what happened and when.

Significant research interest and activity around Fibrinogen

- Key Opinion Leading researchers are working to demonstrate that Fibrinogen plays an even more important role in the clotting cascade than currently understood

- Clinical trials ongoing, and reporting in early 2019
- The research community is also keen to have a point of care test for Fibrinogen.

A point of care device for Fibrinogen must be easy to use:

- Quick and easy to use
- Robust in use
- Not requiring lots of maintenance and recalibration
- A device for use by First Responders might be different from the device for hospitals.

New competition may be coming:

- A UK-based research group or organisation is rumoured to be developing a similar test. Which may offer information on additional parameters, not just Fibrinogen.

Many front-line clinicians ‘don’t get it’:

- They don’t see value in measuring Fibrinogen on its own
- They don’t see the un-met need
- Or why you would want to use this diagnostic.

Measuring Fibrinogen and ESR in the same device is not compelling:

- The clinicians interviewed were mostly negative about the need for a device combining these measurements.

4. Market opportunity

The Viadynamics team investigated four opportunity areas, where F-Point might be used:

1. Obstetrics
2. Trauma
3. Other surgery
4. Military.

The opportunity for a "2-in-1" Point-of-care (POC) device for the rapid laboratory inflammation diagnostics, which measures Fibrinogen (FG) and erythrocyte sedimentation rate (ESR) in parallel was also investigated.

4.1 Obstetrics

Postpartum haemorrhage is commonly defined as blood loss of 500ml or more within 24 hours after birth. Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries it is the main cause of maternal mortality – World Health Organisation

Maternal deaths from postpartum haemorrhage are rare in the EU and US – less that 1 per 100,000 deliveries as opposed to 150 per 100,000 in the poorest parts of the world. However, the lower figures for the EU and US conceal the fact that for for every death, there are believed to be 10 'near misses' (source: Weeks, 2015, BJOG: An International Journal of Obstetrics and Gynaecology).

Conversations with clinicians suggest that a point of care test for Fibrinogen might be relevant to 1% of births – approximately 90,000 per annum across the EU and US. This analysis is backed up by published research that puts the incidence of PPH at 1.2% of all births (Weeks, 2015, BJOG: An International Journal of Obstetrics and Gynaecology). At 1% of births, and with a use of 3 tests per patient (from conversations with clinicians), that would imply a potential market size – if the test was adopted and used everywhere - of 270,000 tests per annum.

The devices to perform these tests would be located in hospitals with obstetrics departments. The number of such hospitals is difficult to measure accurately. 'Out of date' data suggests that there were 7,500 hospitals with obstetrics departments in the EU and US a decade or so ago, with pressure to close the smaller (less than 100 births per annum) units because of difficulties in recruiting expert clinicians and providing high quality care at such relatively small scale. The Viadynamics team estimates that there are now 1,800 hospitals with maternity

units of significant size (averaging 5,000 births per annum), that constitute the target market for the F-Point device. There is therefore an opportunity to sell to 1,800 hospitals, with the larger hospitals potentially going on to acquire multiple devices over time.

The data used to calculate this level of usage is set out in the table below.

Table 2: summary of obstetrics data

Factor	Data	Source
EU data		
No. of hospitals with significant obstetrics dept. - EU	1,020	Derived from source data by author
Number of births per annum – EU	5.1m	Statistica.com
Avg. no. births per hospital - EU	5,000	Derived from source data by author
Average no of postpartum haemorrhages per hospital	50	Derived by author from interviews with clinicians
Number of F-Point tests used per postpartum haemorrhage case	3	Derived by author from interviews with clinicians
Total number of F-Point tests p.a.	153,000	Calculated from data above
US data		
No. of hospitals with significant obstetrics dept – US	780	AWHONN, USA
Number of births per annum – US	3.9m	Centres for Disease Control and Prevention (CDC, US)
Avg. no. births per hospital - US	5,000	Derived from source data by author
Average no of postpartum haemorrhages per hospital - US	50	Derived by author from interviews with clinicians
Number of F-Point tests used per postpartum haemorrhage case – US	3	Derived by author from interviews with clinicians
Total number of F-Point tests p.a. - US	117,000	Calculated from data above
Total – EU and US		
Total number of F-Point tests p.a. (EU plus US)	270,000	Calculated from data above

Pregnant women also have their bloods taken at the time of registering with the maternity hospital. This panel of tests may or may not then be repeated before delivery. These tests involve blood being sent to the laboratory, and a von Clauss device being used to measure Fibrinogen level. The F-Point device is unlikely to be used instead of the von Clauss assay for

this work, and the team at DCU have in any case been focused on developing an 'accurate enough' test that is 'quick and easy' for point of care – rather than trying to take on and replace the 'gold standard'.

Overall, the addition of a point of care test for Fibrinogen would be welcomed by clinicians. It would enable them to engage in more 'evidence-based medicine' as opposed to 'trial and error' in addressing a serious medical event with life-threatening potential.

4.2 Trauma

Clinicians have confirmed that F-Point might be used in the Emergency Department, where patients may be bleeding internally as a result of gunshot or stab wounds, or from injuries sustained in road traffic accidents. Desk research has confirmed that 'falls from a height' are another source of these injuries.

Trauma is a major cause of death, and the leading cause of death among young males in developed countries. In the UK, trauma deaths from 'major haemorrhage' and 'massive haemorrhage' are running at over 2,000 per annum (source: Royal London Hospital). Extrapolating this death rate would mean 16,500 death per annum across the EU and 10,500 in the US – a total of 27,000 – from trauma haemorrhage.

Gun and knife injuries

Fortunately, gunshot injuries are relatively rare occurrences. Data between countries is not easily comparable, but it appears that the number of fatal shootings in the US (at over 11,000 per annum, excluding deaths from suicide*) is significantly higher than the total number of murders in all of Europe (5,900 per annum). In addition to the 11,000 'murders' in the US, there are an additional 22,000 fatal shootings per annum that are classed as suicides. There are a further 73,500 victims of gun crime in the US, whose injuries do not prove fatal.

This data would appear to support the hypothesis suggested to us in interviews with clinicians – that demand for F-Point for gun and knife trauma will be higher in those large city-centre hospitals located in areas with high local rates of gun and knife crime.

Stabbing incidents are generally less severe than gunshot wounds – as evidenced by statistics from the UK that 40,000 reported stabbing incidents resulted in (only) 4,600 hospital admissions.

Road traffic accidents

The number of deaths from road traffic accidents (at over 25,000 in the EU and over 37,000 in the US) are higher than the numbers associated with gun and knife crime.

They are also more widely distributed geographically (15% of fatalities in the US are pedestrians (assume mostly in urban locations) and the remaining 85% are drivers or passengers (assume motorway, national route or local road)).

Victims of road traffic accidents are likely to be treated at the scene (by first responders), with those seriously injured being then taken by ambulance to the nearest Emergency Department. A sub-set of the seriously injured will be suspected of having sustained a serious internal injury, and so the F-Point test becomes clinically relevant.

Forecasting demand for F-Point

There are 11,600 Emergency Departments in operation across the EU and US, and each is a potential buyer of an F-Point device. Usage per department is difficult to predict. Some of the clinicians we spoke to suggested 1-3 cases per week per department. Taking the mid-point (2 cases per week, 100 tests per annum) yields a potential market opportunity of 1.16m tests per annum.

The data used to calculate this level of usage is set out in the table below.

Table 3: selected data on gun and knife crime, road traffic accidents

Factor	Data	Source
Gun and knife crime		
No. of murders (Europe)	5,934	UN and WHO data
No of fatal shootings in US (excluding suicides)	11,208	Centres for Disease Control and Prevention (CDC, US)
No. of non-fatal shootings in US	73,505	CDC, US
Total shootings	84,713	CDC, US
No. of stabbings – UK	40,000	ONS, UK
No of hospital admissions as a result of stabbing - UK	4,656	ONS, UK
Road traffic accidents		
Deaths from road traffic accidents – USA (2016)	37,461	US National Highway Traffic Safety Administration
Deaths from road traffic accidents – EU (2017)	25,250	European Transport Safety Council
Number of Emergency Room departments in US - 2015	5,273	Emergency Medicine Network
Annual no. deaths from road accidents / no. of Emergency Depts. (USA)	7.1	
Estimated number of Emergency Departments - EU	6,300	
Summary data – gun and knife crime		
Number of hospitals with significant cases of gun and knife crime	500	Calculated by author
Number of cases per hospital per annum	50	Calculated by author
Total number of tests (gun and knife crime)	50,000	Calculated by author
Summary data – road traffic deaths		
Number of Emergency Departments – EU and US	11,600	Calculated by author
Total number of tests per hospital p.a.	100	Calculated by author
Tests per patient	1	Calculated by author
Total number of tests	1,160,000	Calculated by author

4.3 Other surgery

The Viadynamics team discussed the use of a point of care test for Fibrinogen during other surgeries.

These are planned procedures, and the surgeon organises a series of blood and other tests to run in parallel with the main surgery, to provide the information that the surgeon requires to monitor the patient and the progression of the procedure.

These tests are multi-parameter, and are conducted using devices such as the ROTEM.

We concluded (in consensus with the clinicians that we interviewed), that a point of care test, for one parameter, would not have a compelling USP for these planned procedures.

4.4 Military

The Viadynamics team interviewed clinicians that work with the military sector, who indicated to us that F-Point would be of interest to military organisations. This application can be thought of as an adjunct to the 'trauma' opportunity described in section 4.2 above – in this case dealing with trauma injuries from gunshots and explosives sustained on the battlefield.

It is difficult to predict demand – which is likely to be high when there is a war on, and low during peacetime. Interest in medical innovation for military applications appears to follow this 'on-off' switch – there was considerable interest during the wars in Afghanistan and Iraq, less so now that these conflicts have ended.

Wounded soldiers are normally evacuated to military field hospitals located behind the 'front line'. Surgeons based at these units quickly build deep expertise on the complex injuries sustained in armed conflict. A point of care test for Fibrinogen level, such as F-Point, is likely to be adopted by forward-looking military organisations, for use in these field hospitals.

4.5 "2 in 1" diagnostic

The opportunity for a "2-in-1" Point-of-care (POC) device for the rapid laboratory inflammation diagnostics, which measures Fibrinogen (FG) and erythrocyte sedimentation rate (ESR) in parallel was investigated with clinicians, who were not convinced by the possibility of combining these two tests in a single device.

5. Development and regulatory overview

The F-Point team have successfully demonstrated that their measurement principle works, and their clinical trial will furnish supporting evidence in a clinical setting. This should allow them to raise funding to develop the commercial device along with trials to demonstrate its efficacy.

5.1 Design choices

The next stage of the project is crucial in navigating the regulatory hurdles and making the design decisions to ensure they produce a device which fits the market requirements. It can be tempting to make decisions quickly in the interests of making progress but in fact careful decision-making is essential to the overall success of the project. During the next phase of the project the team must make decisions about what the device will do and how it will do it. For example, it is likely that the system will consist of a disposable sample cartridge and a reusable Reader. Should the disposable include a lancet to permit a user to collect a blood sample or should it rely on the use of a third-party lancet? The former option simplifies usage of the system but is likely to increase the regulatory class of the device and introduces safety hazards which need to be mitigated.

Currently the system requires users to undertake simple operations to reconstitute reagents and mix them with the sample. Typically point-of-care devices automate 'wet-chemistry' steps and seek to simplify usage as much as possible. For this reason, it is likely that all reagents should be contained with the disposable. It may be possible to introduce the sample into a chamber in which a dried reagent has been lyophilised (thus maximising shelf life). Alternatively, the disposable might contain a liquid reagent, (likely to result in a more limited shelf life), or a dried reagent which is reconstituted by a buffer solution, (a disposable containing both dried reagents and liquid buffer is the most challenging combination from the point-of-view of achieving acceptable shelf-life).

The actuation of steps to motivate and mix reagents could be achieved using some manual interactions, (pressing of blisters, etc), - simplifying the system and reducing cost. However, this introduces risk of user-error, so it may be best to automate usage as much as possible. An examination of current (or similar) workflows should identify usage which is most familiar to users and minimises disruption of current ways of working. For example, simply requiring users to insert a sample vacutainer into the reader.

By way of comparison it is worth examining the design decisions of a similar system by start-up Vivacta, which was eventually commercialised by Novartis as the *Niji* platform.

A whole blood sample was obtained with a 3rd party lancet and introduced straight into the disposable using a capillary channel. The disposable itself was an injection moulding assembled with multiple layers of materials. Reagents were lyophilised into a cascade of chambers which encouraged turbulent flow and mixing.

When introduced, the sample was contained within a visible loop of channel which reduced the risk of the user not collecting sufficient sample, (a key failure risk). The cartridge engaged with a pump, contained within the reader, which moved the sample. In this way the sample was initially moved backwards and forwards to ensure mixing, before moving it on to the optical windows where the measurement took place.

The design decisions will be different for F-Point, but it is essential that they are made carefully to maximise the chances of success.

Project risks are most likely in relation to usability and the design of the disposable. A user centred design process which seeks to objectively assess user-needs and workflows is essential. Design decisions should be made in the context of these user-needs and verified with frequent user testing as the concept is developed. Scope should include a wide definition of who the user is, (for example the person required to maintain and clean the device), and the full cycle of its use, (from storage of disposables to their disposal). Typically, early prototypes are CNC machined which permits rapid and cost-effective development at the risk of machining artefacts interfering with fluid flow. It is important to verify the design early on with at least a prototype injection moulded prototype.

Materials and construction methods should be chosen which allow the system to meet requirements while minimising cost. The use of a disposable in any medical system permits flexibility in the business model, (for example the use of the ‘Gillette model’ of a relatively expensive disposable reducing cost of adoption). In the case of F-Point it is easy to imagine a single injection moulding combined with flat sheets to create a low-cost solution. Surface

treatment can be used to increase hydrophilic properties, promoting capillary flow while widening choice of materials.

5.2 Roles and responsibilities

The building of the development team will often include a number of third-party experts:

- Regulatory consultant – a key partner who devises regulatory strategy and supports certification of both device and start-up company. This can be a time consuming and expensive job. Some consultants take a hands-on approach and others minimise cost by helping the client to do much of the work themselves using template documents.
- Product design - many design teams have expertise in the design of microfluidic point-of-care diagnostic systems. Where separate mechanical and electronic/software companies are chosen, it is important to ensure there is a clear chain of responsibility.
- Prototyping vendors – usually recruited and managed by the design partner in consultation with the client.
- Component manufacturers – best selected by means of a dedicated tender process.
- Contract manufacture – will take overall responsibility for the supply chain and can provide fulfilment and management of returns. Generally, the 'legal manufacturer' will be the start-up company though this role can also be sub-contracted.
- IP lawyer – Freedom to operate (FTO) and IP is essential for any start-up. However the temptation to file early should be examined. Costs to support filings can fall at a time when the emerging start-up is short of money and filings can often be made irrelevant by technical developments later in the project.

Some contract manufacturers also offer design services. While this can be a cost-effective solution, it is essential to ensure that the resulting design is portable (i.e. can be switched to another manufacturer with minimal disruption), and is not optimised to the particular manufacturing technologies offered by that company. It is worth noting that the opportunity to hold a tender to manufacture components and assembly may be lost.

Regulatory approval

The regulatory consultant is a key partner for any medical start-up. They are essential in forming the regulatory strategy and minimising regulatory barriers. A key document is the 'intended purpose' which sets out what the device will do and who is defined as the user. A regulatory barrier to be minimised for an IVD might include classification as a measurement device, which would then necessitate verification by a notified body (rather than self-certification). For that reason, IVD companies often adjust their intended purpose to provide users with metrics which are dimensionless.

Product development should seamlessly integrate regulatory activities so that a suitable Technical File is assembled as the project progresses. It is essential that risk management is integrated as an activity as early as possible. Similarly, the definition of requirements in the product requirements specification (PRS) must be verifiable and relevant. At the verification stage of the project each requirement must be shown to have been met.

In the coming few years the In-Vitro medical devices Regulation (IVDR) will replace the current In-Vitro Medical Devices Directive, which will have significant implications for medical start-ups such as F-Point, (mainly in the area of clinical validation and the role of notified bodies). Both the consumable and the instrument are likely to be classified as being in-vitro diagnostic (IVDs). However only the consumable has to be in the patient environment (i.e. the patient can touch it), so we have the opportunity to have the instrument tested to IEC 61010 (safety of laboratory equipment) rather than IEC60601 (safety of medical devices). It is preferable to use a third party lancet rather than incorporate a needle into the disposable, otherwise you would again increase the classification of the device.

The Legal Manufacturer is the body placing the device on the market in the EU. This typically means that a start-up must plan to become certified to ISO 13485, a process standard that defines how medical devices are designed and manufactured. This generally requires a Quality Management System (QMS) which covers a wide range of activities from design control to vendor selection.

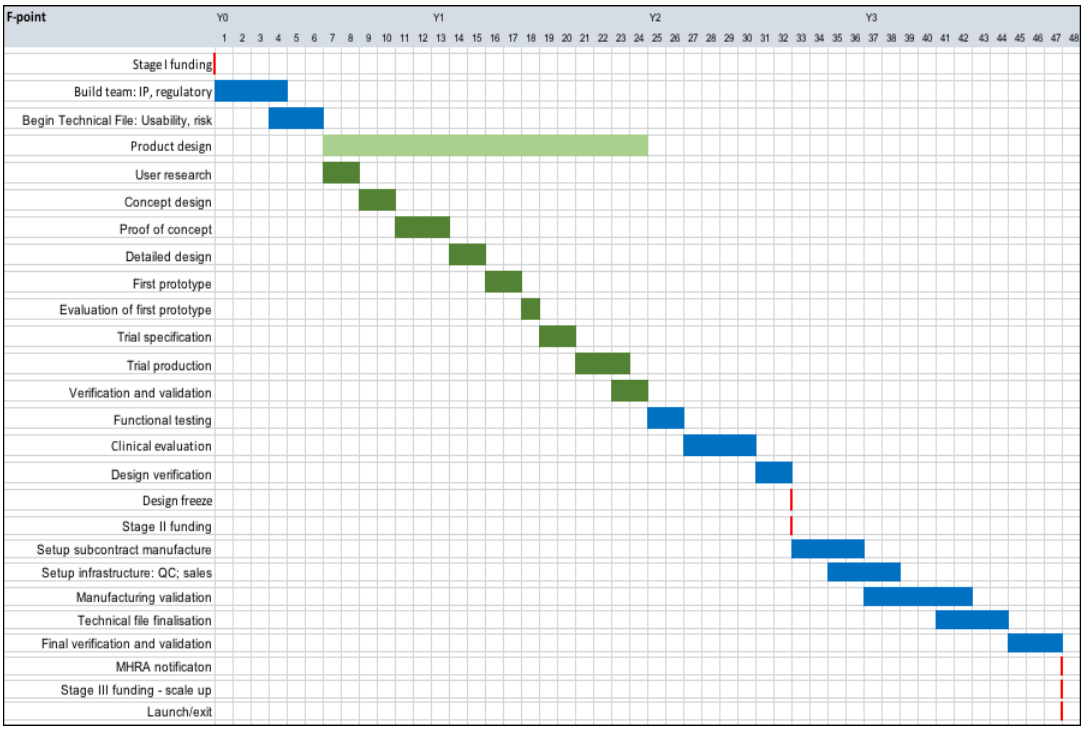
Regulatory strategy should include a plan to address US and ROW markets. Separate regulatory consultants with experience in these regulatory regimes will need to be recruited.

5.3 Milestones and tasks

The Gantt chart below is an illustration of the typical timeline for medical device development. Exit can occur at multiple points in the journey but is maximised when risk is minimised at the endpoint. Activities have been split into two phases:

- Phase 1 activity consists of product design (including testing and validation) up to ‘design freeze’ when the final product is confirmed
- Phase 2 consists of preparing for launch

Table 4; GANTT chart



In many ways this timeline is idealised and will be subject to many options and variations, however it contains most of the relevant tasks and milestones.

On securing Stage I funding, a start-up needs to set about forming a suitable team, which includes internal members such as CEO and CTO, but also external subcontractors, such as regulatory consultants and designers (if this is not done internally).

The Technical File (TF) is initiated, built around the intended use, risk management and a first draft of the Product Requirement Specification (PRS).

Product design can take as little as 12 months, but often a lot longer. It is broken down into numerous sub-tasks, (shown in green). User research is the starting point for any user-centred design process, this informs the PRS as well as serving as the inspiration for design concepts. As the design solution is developed it should be verified by review with representative users and testing where possible. Proof-of-concept testing using simple, limited test-rigs helps to reduce technical risk and optimise the design. Detailed design of a first prototype is followed by its manufacture using low set-up cost processes such as CNC machining and 3D printing. It is important to thoroughly test this prototype to highlight shortcomings. A pre-compliance review for electrical safety and RFI with a test-house is recommended and a thorough review of risk. A design iteration, (to implement changes

arising from the reviews) leads to the preparation of a Trial Specification, - a complete set of drawings, bills of materials, etc. The production of units for use in the clinical evaluation should include representative manufacturing processes (such as injection moulding) and assembly to detailed assembly instructions and test procedures. Design verification, where outcomes are compared to the testable requirements in the PRS, is followed by a design freeze.

Stage II funding permits the set-up of the supply chain and infrastructure to place the device on the market. After validation of the manufacturing process and finalisation of the technical file, final verification and validation is followed by notification of the MHRA and CE certification. At this point, risk is minimised and there is an opportunity for Exit or further funding to scale production and distribution.

5.4 Outline costs

Cost estimates are provided below, broken into two phases, and including the 'team' and other costs in addition to the product design and development activities set out above.

Table 5; outline costs

Activity	Cost
Phase 1	
Design (mechanical, electronics and software)	€500-700k
Tooling	€25k
Development materials	€30-50k
Test house fees	€25-30k
Project management & other internal team	€100k
Total for Phase 1	~ €800k
Phase 2	
Contract manufacturer	A combination of set-up fee and manufacturing contract. Will vary from product to product
Tooling	€100k
Test house fees	€25-30k
Regulatory consultant	€60-85K
Cost of clinical trial	€?
Internal team	£150k
Overheads (space costs, insurance, etc.)	€40k
Total for Phase 2	'Rough' estimate ~ €650k
Grand total; Phases 1 & 2	~€1.5m

Based on these costs, plus our estimates for material costs and assembly of the finished product, we anticipate that F-Point will have a final cost per unit of well below €1,000.

6. Business Model and strategy

The Viadynamics team has investigated the opportunity to commercialise the F-Point device.

6.1 USP

Against the current competitive set (von Clauss, ROTEM, TEG), F-Point has a number of advantages. Three of these are compelling enough to constitute a unique selling proposition (USP), as set out in the table below.

Table 6: USP of F-Point

USP of F-Point	Performance of competitors
Rapid result (c. 6 minutes) enables clinicians to make better prescribing decisions, with more confidence	Von Clauss will take from 35 minutes to 2 hours, depending on the hospital set up. TEG / ROTEM requires a skilled and experienced user
Easy to use (simple operating procedure, whole blood compatible, small blood volume of 40uL)	ROTEM especially difficult to use. Von Clauss designed for use by laboratory personnel, not point of care staff. Both require sample preparation
Robust device, suitable for use outside of the hospital laboratory	ROTEM is more fragile, and requires re-calibration if knocked about. TEG requires PC connection and wet chemistry space. Von Clauss device is a laboratory test, requires sample preparation

6.2 Quantifying the market opportunity

F-Point will generate sales from both the device, and a consumable. The total market opportunity for consumables is valued at €14.3m per annum. The supply of devices to the 13,400 hospital departments where F-Point might be used can grow to €8.0m per annum at maturity. The total market opportunity is therefore €22.3m per annum.

The Viadynamics team have used a sales price of €10 per consumable in these calculations. Previous analysis by Reimbursement Strategies LLC for the F-Point team identified a likely reimbursement amount of $14.02 in the US, while the F-Point team predict a manufacturing cost of less than €2 per test. A sales price of €3,000 per device has been used in our financial modelling.

The F-Point team is expected to spend two years developing and optimising the device, and a further year working with a small number of Key Opinion Leaders (KOLs) to develop sufficient data on the performance of F-Point in use, and the clinical value that it delivers. Once this is complete, F-Point can be launched, with its chances of commercial success maximised.

Obstetrics

A 5-year sales forecast has been prepared, showing revenue from device sales, and test sales. After 5 years, annual sales have increased to €3.33m. The model assumes that 80% of hospitals purchase a device, and that a competitor emerges, with both devices achieving market share of 50%.

Trauma

Potential usage in trauma is higher than in obstetrics – there are more Emergency Departments and trauma victims that there are cases of postpartum haemorrhage. After 5 years, sales can increase to €9.6m. Again, the emergence of a competitor is anticipated, and an equal split of market share is factored into calculations.

Aggregating the total opportunity

The revenue opportunity for F-Point, pursuing each of these opportunities, is set out in the table below. Forecast revenues in 'Year 5' after launch are €12.9m.

Table 7: sales revenue, all applications

	Year 1	Year 2	Year 3	Year 4	Year 5
Obstetrics					
Revenue from device sales (€m)	0.45	0.45	1.35	1.35	2.25
Revenue from test sales (€m)	0.14	0.27	0.54	0.81	1.08
Total revenue (€m)	0.59	0.72	1.89	2.16	3.33
Trauma					
Revenue from device sales (€m)	1.45	1.45	4.35	4.35	7.25
Revenue from test sales (€m)	0.29	0.58	1.16	1.74	2.32
Total revenue (€m)	1.74	2.03	5.51	6.09	9.57
Total revenue – all applications					
Revenue from device sales (€m)	1.9	1.9	5.7	5.7	9.5
Revenue from test sales (€m)	0.4	0.9	1.7	2.6	3.4
Total revenue (€m)	**2.3**	**2.8**	**7.4**	**8.3**	**12.9**

6.3 Development and pre-launch costs

The Viadynamics team recommends manufacturing a first batch of approximately 20 devices, to be used to fully test and validate the device with the research community and with KOL clinicians in obstetrics. Subject to successful progression, tooling can then be put in place to manufacture larger batches, with the aim of producing 500 devices in advance of product launch.

The costs associated with this activity are likely to run to a total of €1.5-2m.

6.4 Alternative business models

The Viadynamics considered two alternative business models for the commercialisation of F-Point:

1. License to an existing manufacturer and supplier of in vitro diagnostics (IVD) devices
2. Form a start-up company to develop, launch and market F-Point.

Key criteria used in evaluating are:

- Size of the prize – how large and compelling is the opportunity? How much is it going to cost to get to it?
- De-risking – what are the key milestones along the way? When are the key risks removed?

Size of the prize

The creation of a new market segment, valued at up to €22.3m, is likely to be of significant interest to the incumbent diagnostics companies.

However, there are a number of technical and market risks that mean these companies are unlikely to want to acquire or license F-point at this time, plus short-term pressure to hit sales targets mean that a medium/longer term opportunity like F-Point will not be pursued.

The incumbent companies are therefore likely to prefer to adopt a watching brief, as F-Point is developed and as the market potential is proven.

De-risking

The Viadynamics team believes that the F-Point team are likely to be able to resolve the remaining technical risks, and produce a 'market-ready' device.

The key risks appear to be market-related, rather than technical. How big is the opportunity? What will be the future competitive set? How much of the opportunity can F-Point capture?

The key activities to de-risk the development and commercialisation of F-Point are:

- Engage with the appropriate development and regulatory suppliers and partners
- Develop a product that is optimised for use at point of care, and superior to any competing devices that emerge
- Work with Key Opinion Leaders to confirm that F-Point adds significant clinical value
- Use device prototypes to engage with clinicians and refine the estimate of market potential.

6.5 Recommendations on commercialisation strategy

The Viadynamics team recommends that the F-Point team continue to develop the device at DCU and work towards placing the device into a start-up company. This would be subject to continued progress on technical development, engaging strongly with leading researchers in the field and KOL clinicians, and (through these interactions) further validating the opportunity and confirming F-Point's ability to take the market leadership position, should competing products emerge.

A license to, or marketing agreement with, to existing supplier of in vitro diagnostics could be explored later, in order to maximise the ability to reach 100% of the market.

7. Appendix 1 – notes of KOL interviews

The Viadynamics team interviewed a number of Key Opinion Leading (KOL) researchers and industry experts. These people are listed in the table below.

Table 8; people interviewed

KOL	Organisation
Dr. Patrick (Patch) Thornton	Rotunda Hospital, Dublin
Dr. Roger McMorrow	Clinical Director & Consultant Anaesthetist National Maternity Hospital, Dublin
Prof. Fionnuala Ní Áinle	Consultant Haematologist, Mater Misericordiae University Hospital and Rotunda Hospital, Dublin
Professor Beverley Hunt	Director of the Haemostasis Research Unit, Guy's and St. Thomas's Hospital Trust, UK
Dr. Nicola Mutch	Institute of Medical Sciences Aberdeen University
Dr Win Sen Kuan Dr Kanwar Sudhir Lather	Emergency Medicine Department National University Hospital, Singapore
Prof Charmaine Childs	Professor of Clinical Science Sheffield Hallam University
Oliver Tang	GP and medical technology expert Shanghai, China
Dr Brendan McGrath	Senior Lecturer University of Manchester.
Dr Kyle Stewart	Torbay and South Devon NHS Foundation Trust

Notes of these conversations are set out below:

Dr. Patrick (Patch) Thornton
Rotunda Hospital, Dublin

Fibrinogen level is elevated in pregnant women, in preparation for clotting after bleeding during childbirth. All women bleed at birth, but normally only a small volume.

When Fibrinogen in pregnancy drops below 2g/L – there is a 99% chance of a major haemorrhage. Closer to 4g/L than 2g/L would be normal.

When we have an ongoing bleed, we need to measure the fibrinogen level quickly. We take a blood sample, we print the stickers and label it. We send it to lab and wait 35 mins or more for a result. Fibrinogen begins to be consumed as part of the clotting cascade. The case has moved on. An obstetric haemorrhage is a fluid case and the parameters move quickly.

We would see 30-40 cases of major PPH per annum in the Rotunda.

When we have a bleed…….
We give fluids to get blood volume up. We also give red blood cells plus Fibrinogen. We rarely give platelets.

Research interest
Fibrinogen is the new hot topic in obstetrics. Evidence is likely to build that shows giving Fibrinogen early has positive outcomes here also. There is a multi-centre study currently recruiting in France.

The evidence base around administering Fibrinogen is not complete – as trauma and pregnancy are not easy places to do clinical trials. You are dealing with emergency cases – not planned procedures or chronic conditions.

Competing tests
The Von Clauss assay is a laboratory test, and is not point of care. You need to centrifuge the blood to obtain the plasma. It all takes time, and the result comes back to us electronically after about 35 minutes – by which time levels will have changed. In a general hospital, waiting times would be longer.

All patients have their ‘booking bloods’ taken at 12 weeks of pregnancy. This is performed using the von Clauss assays. At this hospital, we would have 8,000 per annum. A second test is then carried out (again using the Von Clauss) at 32 weeks.

I don't see the point of care device being accurate enough to replace the von Clauss assay for these use cases. Instead, it will be used on the major bleeds, as they occur. Up to 100 cases per annum in this hospital. And we will continue to send samples to the lab, for completeness.

The ROTEM gives a fibrinogen result and a curve showing coagulation. Tells you to give more Fibrinogen or more platelets. It is a very user-unfriendly device – it takes 20 minutes to load. Turnaround is 20 minutes. You need space and you need quite significant training. We got a ROTEM in Mater in 2009, and I had used it in London previously. Frequently mess it up. Never had confidence in myself doing it, or in the result I get. One guy in the Coombe uses it. Rotunda said 'no' to getting one.

Speed versus accuracy

The point of care device does not need to be totally accurate. The difference between 4.1 and 4.2g/L is not relevant. We need to know if the level is very low, low or normal.

Other uses, outside obstetrics

The major uses of this POC test are likely to be obstetrics and trauma.

In cardiac surgery, bleeding is common. But you have a little more time to deal with it. We give heparin to slow clotting and then reverse this at the end of surgery. Use of Fibrinogen in cardiac surgery is increasing, but not as fast as in obstetrics. There is not a huge amount of evidence for its use, yet. This may build over time (or not).

Dr. Roger McMorrow
Clinical Director & Consultant Anaesthetist
National Maternity Hospital, Dublin

We will give Fibrinogen where there is 1500ml or more of haemorrhage – there are 120 such cases per annum in the hospital here.

About half the cases come from planned caesarean procedures (we have a caesarean rate of 20% in the hospital) and the other half are emergency caesareans that come to us from the labour ward.

We administer the Fibrinogen and then test for the Fibrinogen level, wait for the lab test to comes back - but this is not fast.

A bedside test would guide how much Fibrinogen to give.

Over the course of a surgery with a bleed, I would give from 2g to 12g of Fibrinogen – which comes in a 1g bottle.

In fast evolving haemorrhage, info from a lab test will be out of date. So a faster test is ideal.

Once the bleed starts, I would administer 2g of Fibrinogen, and send bloods to the lab to measure the Fibrinogen level. If that comes back below a certain level (2g/L), I would continue giving. The normal range is between 4-6g/L. I would be aiming to get to 4g/L.

For elective caesareans – we would have full bloods including Fibrinogen level available to us.

It's a dynamic event and the bleeding patient is using their Fibrinogen. I would potentially perform the test 3-4 times per patient – as its dynamic and changing.

I will also be doing other tests – and will still need to send blood to the lab during a haemorrhage.

Cost of Fibrinogen is not an issue, and it is not expensive. I have no idea what it costs, and there is no pressure to minimise use (and therefore cost) of Fibrinogen.

The device

How will this new machine fit into our workflows? Who will maintain it? How simple of complex will it be?

If it is simple and easy, like a blood sugar analyser for monitoring glucose – then easy to fit in.

If it is another complex, stand-alone machine – like ROTEM is – that will be more difficult. It took us almost two years to get the ROTEM device approved, funded and to get our lab to take it on as a point of care device and maintain it for us. It's a sensitive machine that cannot be moved, and that requires servicing.

If it needs maintenance - the lab people do not like having to validate and certify devices that are outside their lab. People knock it around, bump into it – and then the lab people get blamed for it being off. The lab people will not like a 'finicky' machine.

Selling in a new machine that measures only one thing – this will be hard. We take a blood gas analysis during a haemorrhage – if this was one more line on a blood gas print out, that would be valuable.

Conclusions

Overall – useful, but not a game changer as it measures only one component of what we do in a haemorrhage.

To be useful, a test needs to make you do something different. We already get Fibrinogen level, but it takes longer. Would this allow you to do something different? Would it enable you to give Fibrinogen earlier? No. Would it let you decide how much Fibrinogen to give, earlier. Yes. So, it would be useful in guiding your subsequent doses fibrinogen. It will quickly tell if I need to be aggressively giving more, or if the Fibrinogen level is OK and that I need to be looking at something else.

How will the machine fit into current workflows? Who will maintain it? Can you build it into an existing machine, or make it as simple as a glucose monitor?

Prof. Fionnuala Ní Áinle

Consultant Haematologist, Mater Misericordiae University Hospital and Rotunda Hospital, Dublin

Severe bleeds in women are potentially lethal. That the death rate is as low as it is down to exceptional standards of medical care.

Once a bleed occurs, the various protocols in place kick in, and must be followed:

- Almost everyone will get TXA. The clinical value of TXA was confirmed in the WOMAN clinical trial, and subsequently appeared as a landmark paper in the Lancet
- Fibrinogen replacement is indicated when Fibrinogen is likely to be low – when haemorrhage is due to an amniotic fluid embolism or an abruption. It is not indicated when the cause is uterine atony (floppy uterus).

Once a bleed starts, the Fibrinogen level can collapse, in seconds.

Because the Rotunda is a small hospital, and focused on obstetrics, we can turn a Fibrinogen test around quickly. The Mater, in contrast, is a large general hospital, and it can take 1-2 hours for a result.

Looking at Health Technology Assessment;

- TXA is relatively cheap
- Fibrinogen replacement is quite expensive – hundreds of euro per gram. If clinicians are overdosing to be on the safe side, then a point of care test for fibrinogen would be cost saving as well as having clinical value.

Overall, I see a need for a point of care test for Fibrinogen, and I think that F-Point is very exciting. I don't believe that the ROTEM device is a suitable alternative to a device such as F-Point.

Professor Beverley Hunt

Professor of thrombosis and haemostasis and Director of the Haemostasis Research Unit Guy's and St. Thomas's Hospital Trust, UK

Beverley considers herself a world expert in this area. She is already working with Louise Kenny.

There is a lot of work in trauma showing low fibrinogen level at admission.

Just completed a trial using thromboelastography (TEG). Peter Collins in Cardiff has looked at use of thromboelastography in PPT, also measuring FB. Shown it is useful. Got use of TEG adopted in Wales. She recommended speaking to Peter.

She things F-Point could replace this with its point of care test.

Ongoing research

There is significant ongoing research in this area:

- Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (iTACTIC) will publish results in 6 months from now – on how to better treat patients who bleed. See: http://www.c4ts.qmul.ac.uk/research-programmes/itactic
- She is about to publish a paper on military use.

Competition

Beverly wanted to know more about F-Point method as ROTEM FG level is influenced by haematocrit levels (density of red blood cells in blood). Wondered if it was different to ROTEM in measuring FG. Was it just measuring clotting?

In France they have a different approach. They perform an INR (the prothrombin time (PT) is a test that helps evaluate a person's ability to appropriately form blood clots). The international normalized ratio or INR is a calculation based on results of a PT that is used to monitor individuals who are being treated with the blood-thinning medication (anticoagulant) warfarin.

Doctors who are saying 'no'

She thought they were mistaken – as when they have a patient who 'bleeds out', then standard treatment of TZA switches off ability to break down clot.

Conclusion

Thinks there is a huge opportunity - every trauma centre needs a Fibrinogen monitoring device.

There is a trend is to pre-hospital trauma care. Patients given blood components immediately by paramedics. Is the test suitable for going in the ambulance?

Military applications also relevant - any situation with excessive bleeding.

We should be aware that there are other near patient tests coming out capable of measuring FG. May have hinted that this test provides information on more than just Fibrinogen level.

Dr. Nicola Mutch
Institute of Medical Sciences
Aberdeen University

Nicola's particular area of interest is Fibrinogen structure and clot stability.

Fibrinogen is used up faster than other factors in blood clotting, so it is important to be informed about how to reconstitute levels. Current methods take time so a POC device would be useful.

She wanted to know if F-Point just measured concentration or whether it would give any indications on structure. This varies apparently and can have a big impact on how easily a clot degrades or becomes loose. This can be a big cause of acute blood loss, and so her work is focused on trying to understand this.

She could see this device being useful in any surgery which risks high blood loss: Hip surgery is common and some patients have profound blood loss; Coronary bypass surgery; Liver transplant; Trauma surgery - testing patients in the ambulance would be good. Currently use of transexamic acid (TXA) is recommended (part of the emergency pack) but it doesn't do anything about FG levels, which may need to be supplemented. Previously they used to just use plasma but this dilutes the blood. Ideally, they want to give more concentrated FG, so knowing Fibrinogen at the POC would be advantageous.

Any trauma surgery can have risk of blood loss. It can be hard to tell.

ROTEM and TEG are essentially doing the same thing but are made by different companies. There are advantages to a 'global' test but it means the results have to be dissected to understand which parameters are relevant.

Maternal bleeding at childbirth still happens but is generally well managed in the UK.

She though a POC device for trauma in ER would be good for situations where TXA has been administered but patients are still bleeding.

Doesn't see the usefulness of as a pre-op test unless there is a particular reason to suspect a problem. Its just a matter of time and money being spent on better things. There may be value in certain scenarios.

She was a bit dubious about the <2 g/L assertion. FG levels are normally 3 g/L so felt 2 was a bit arbitrary. Pregnant women are not 'normal' patients and their levels can be 'all over the place'.

She felt there is an emerging understanding of Fibrinogen in clotting. She comes at it from a basic science direction. Clinicians have a different point of view. ROTEM and TEG have been around since the 70s and have only relatively recently taken off. It takes time to convince clinicians that something is useful. A case had to be made for even the use of TXA as there are some side effects and risks.

She would be interested to hear about the results of the trial and would like to trial F-Point in a project she is setting up for trauma surgery. They are currently putting a grant application together and would like to use F-Point to quantify FG. They are looking at Fibrinogen structure and its effect on clotting.

Also thinks there is potential for Fibrinogen and ESR device. Fibrinogen is an inflammation protein.

Ideally, she would like to measure Fibrinogen concentration and downstream clot formation. Is there a way of incorporating the measurement of speed and structure of clot formation?

Dr Win Sen KUAN
Senior Consultant
Emergency Medicine Department, National University Hospital, Singapore

Dr Kanwar Sudhir Lather
Associate Consultant
Emergency Medicine Department, National University Hospital, Singapore

A point of care test for Fibrinogen has value in the Emergency Room – where the patient is bleeding heavily in trauma surgery in emergency department - and we need more information.

We do not currently measure Fibrinogen, and don't give Fibrinogen without knowing the levels, as it's a very expensive product to give. We resuscitate with blood products (transfusions) – and any info that allows us to do this more targeted is welcome. Only 7 minutes turn around means we would use before surgery starts. We give transfusions to replace lost blood, then the patient goes into surgery to repair the damage that is causing the haemorrhage.

Will not use the test as a screen – will only be used on trauma patients who are bleeding. As they bleed, Fibrinogen levels start to drop, and they need a top-up.

We perform PTI and R-bases test on trauma patients. Fibrinogen test would give more information. If level is low, we can replace Fibrinogen. We have the resources to act on the result (we have the product to replace the levels that are low). Not all hospitals across the Developing and Emerging regions would have this.

The Royal London group are using fibrinogen assays. Measuring Fibrinogen directly, using an optical method.

ROTEM
ROTEM is suitable for use in scheduled surgery. The surgeon plans out the surgery, knows what information they will want, and when. The ROTEM tests are then planned into this.

So, the ROTEM machines sit in the operating suite – for use with cardiothoracic surgery and liver transplant.

ROTEM is not used in the Emergency Department. Not suitable for point of care – too expensive, and too slow to provide the information.

If a severe bleed happened unexpectedly in surgery, then the new device could be used rapidly, alongside of ROTEM.

Conclusions

The proposed test is relevant where there is haemorrhage of any sort, bleeding into an open cavity. This happens in obstetrics, and in trauma.

We would potentially use the assay in the Emergency Department on patients who are seriously injured, requiring large volumes of blood products transfusion. We are an urban ER, in a nation blessed with low rates of gun-knife crime and inter-personnel violence, so our numbers of patients requiring massive transfusions are thankfully low. I would project use of the FG assay 1-3 times a week.

We are interested in running a trial of the proposed device. When there us a usable device that has been validated versus gold standard.

Prof Charmaine Childs
Professor of Clinical Science
Sheffield Hallam University

She started by saying she wasn't fully up to date on the link between Fibrinogen levels and excessive bleeding.

Her first thought was sepsis in ICU - platelets are used up and patients can suffer excessive bleeding. The process she mentioned is disseminated intravascular coagulation - excessive clotting within blood vessels.

She also thought trauma surgery was relevant, (one of her areas of expertise). She defined this as things like road traffic accidents where you can't see evidence of organ eruption or internal bleed due to broken bones. Blood pressure can drop quickly, and patients are clamming and sweaty. Doctors suspect internal bleeding, but it is hard to detect. They generally try to resuscitate with a drip, but the nature of that drip could be better informed.

This might be also something paramedics might use.

She thought excessive bleeding from c-sections is quite rare. She only knew of one case with blood loss greater than 1L. She said that 400 mL is more normal
She feels she is not an expert but didn't immediately see this as an urgent need.

Oliver Tang

Now working in Shanghai, formerly a locum in ER at London hospitals (Charing Cross, St Marys, St Thomas's)

Oliver has a keen interest in, and involvement with, the development of new medical technology.

He wasn't particularly impressed by the F-Point proposition. He said clotting took a lot of components, so didn't see FG levels as being particularly useful.

Not really aware of a problem to be solved, though you might have clotting problems with haemophiliacs and those with liver failure. Usually in childbirth excessive bleeding happens when the placenta ruptures, but you'd just apply pressure to stop bleeding or use a bag of platelets. Internal bleeding is usually in the GI tract. If upper GI the patient will vomit blood. If lower GI they will pass red blood with stool. Fast internal bleeding is usually quite obvious.

They do haemoglobin levels (which is a lab test but takes 10 mins and there are POC devices). They would be interested in Hb level and trends.
Slow bleeding harder to spot but there are symptoms.

Can't see a strong case for F-Point as he is not sure what it really tells you. There could be a variety of reasons for low FB levels.

Dr Brendan McGrath
Senior Lecturer
University of Manchester.

Brendan's perspective was from that of trauma, planned surgery, liver disease and sepsis.

He failed to see the purpose of F-Point. In his opinion FG is just one part of a complicated system, so knowing FG levels (even trends) is not particularly useful, only part of a big picture.

They have TEG machines in ICU and trauma centres. So they can get comprehensive results pretty quickly (30 minutes). He thinks this is not unusual for hospitals. He didn't think something at the point of care (just for Fibrinogen) would make much of a difference.
TEG machines are pretty good, slow and cumbersome but comprehensive in the information they provide. At the Wytheshawe Hospital, they are effectively used as a bedside test.

They have emergency haemorrhage packs so knowing the details of FG is not relevant.
If (as a result of info from F-Point) they want to order specific Fibrinogen products they would need to place an order, send a porter to the blood bank and wait 30 minutes to get it back, so this didn't seem like a feasible approach.

Obstetrics may be another case. They are generally very worried about the risk of major haemorrhage. In the event they have a 'major haemorrhage protocol' in place where they basically pump lots of clotting factors into a patient, so he suspects knowing the FG is not relevant.

ESR is a bit 'old school'. Useful for rheumatic fever and irritable bowel disorders. Its a marker for inflammation. Not used in ICU but maybe occasionally in other areas. He wasn't excited by the idea of a Fibrinogen and ESR instrument.

Dr Kyle Stewart
Medical Doctor and medical technology development expert
Torbay and South Devon NHS Foundation Trust

Seven minutes is quite slow for a point of care test . That's quite a long time for a result. Most point of care tests work in seconds.

In terms of post-partum haemorrhage, 7 minutes is an eternity and we are far more likely to be guided by a patient's haemodynamic parameters, i.e. pulse, blood pressure, respiratory rate etc. Do you know what new usable information knowing a fibrinogen level 7 minutes down the line can give you?

At present there are very well known and well used massive transfusion protocols in all major hospitals that can be triggered, and in this pack comes packed cells, platelets and fresh frozen plasma to replace clotting factors. Are there studies to inform that the fibrinogen sensor is superior to these?

You say "both the von Clauss assay and TEG FF do not address the need for rapid and reliable actionable information on Fibrinogen level in the operating theatre or delivery room" – I would like to see the papers on why there is a need and where its been published.

Fibrinogen is also an acute phase protein i.e. it goes up in inflammation / infection. Does this have any bearing on its ability to give information regarding haemorrhage?

I don't really see the need for ESR. If they are haemorrhaging ESR isn't relevant, and if it's general abdominal surgery ESR will be raised anyway due to the likelihood of concurrent infection / inflammation.

I'm a little dubious on the clinical need for this.

8. Appendix 2 - About Viadynamics

Viadynamics is an innovation consulting firm with a strong capability and track record in business, market, product, service and brand innovation. We have offices in London, UK and Waterford, Ireland.

Our approach combines expertise in business, design and technology to identify and build innovation opportunities. For more than 16 years we have worked with successful corporations, ambitious start-ups and leading universities to drive growth, transform performance and create value.

Figure 1: Viadynamics' corporate clients

Assignments we have performed for our corporate clients include market strategy formulation with brand position migration and product development roadmapping, 'war gaming' the response to breakthrough innovation by a competitor, building the research process 'way of working' for a global corporation after a major reorganisation of its R&D activities, creating business and R&D strategies for clients in consumer, medical and pharmaceutical sectors, building strategies and capabilities for Open Innovation, R&D capability development and leading the innovation teams charged with creating breakthrough products and services.

Viadynamics also works with leading university and public organisations.

Figure 2: Viadynamics' university and not-for-profit clients

Assignments we have performed for these clients include:

- Working with the team at Unicef's Innovation for Children Lab in Copenhagen to measure the impact of their innovation activities and build a portfolio of future innovation for optimised impact
- Performing market validation and feasibility study assignments for a number of universities across Ireland and the UK
- Leading the formation of university spin-out companies, and providing mentoring support to others
- Negotiating license and spin-out terms with universities on behalf of start-up companies
- Working to build, support and expand incubator and accelerator programmes.

Viadynamics also works with a number of SMEs and exciting start-up companies.

Figure 3: Viadynamics' start-up company clients

We have helped these businesses to clarify their propositions to customers, create compelling presentations and investor pitches, access 'soft' funding, secure seed funding, define and pass key value-realising milestones and then secure follow-on funding.