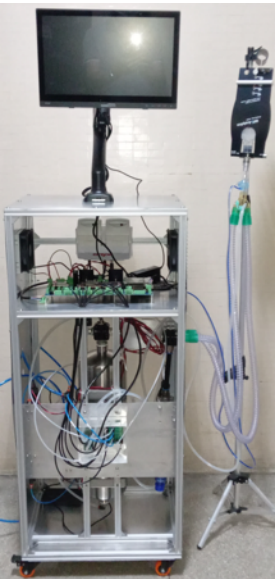
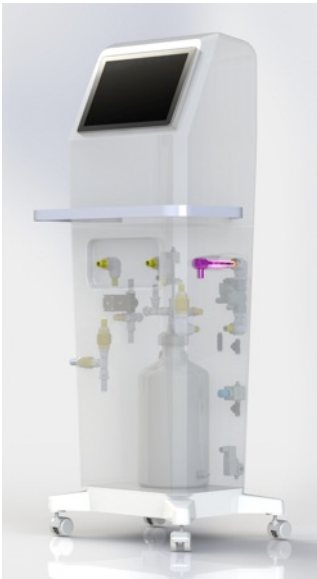
The Ventilator Challenge, 2 years on; the HEV and HPLV response

Part 2: High Performance Low Cost Ventilator, from prototype towards certification



Irina Nasteva
Institute of Physics, Rio de Janeiro Federal University
on behalf of the HPLV collaboration

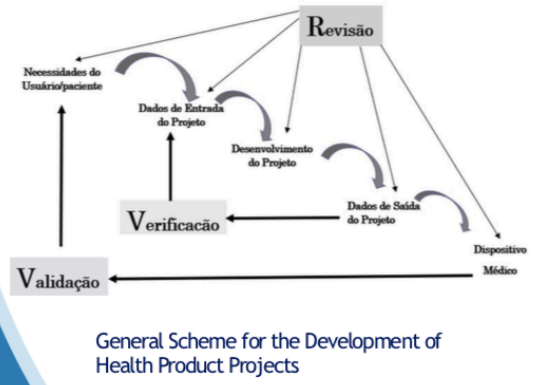
2 June 2022
CERN Knowledge Transfer seminar



How do we get to the industry stage?

- Taking a medical prototype device to the stage of production and commercialisation is a long, complex and costly process.
- Company must prove device compliance with a range of norms and follow procedures.
  - Electrical and software tests.
  - Risk analysis.
  - Safety and efficacy, usability.
  - Medical certification of device by regulatory authority.
  - Product registration procedure.
  - Documentation, ...

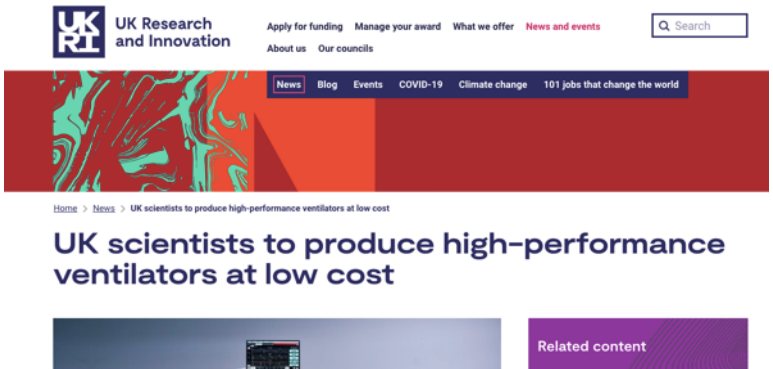
Examples from Brazilian regulatory body ANVISA



General Scheme for the Development of Health Product Projects

The High Performance Low Cost Ventilator project

- HPLV builds on the HEV development with aim of lowering the barrier to industrialisation.
  - Re-engineer hardware with medically-compatible components, optimised design.
  - Rewrite software and test according to regulations.
  - Adapt device for low and middle-income countries, with Brazil as a target.
- The project was awarded funding from the UK Research & Innovation council Global Challenges Research Fund / Newton Fund: Agile Response call to address COVID-19.
  - Targeting low and middle-income countries (from OECD DAC list) likely to be negatively impacted by the pandemic.
  - Project approved in September 2020.
  - Started around the beginning of 2021, ended in April 2022.
- Multidisciplinary team: particle physics, engineering, software and medical specialists.
  - Close collaboration with HEV.



UK Research and Innovation

GCRF
Global Challenges Research Fund

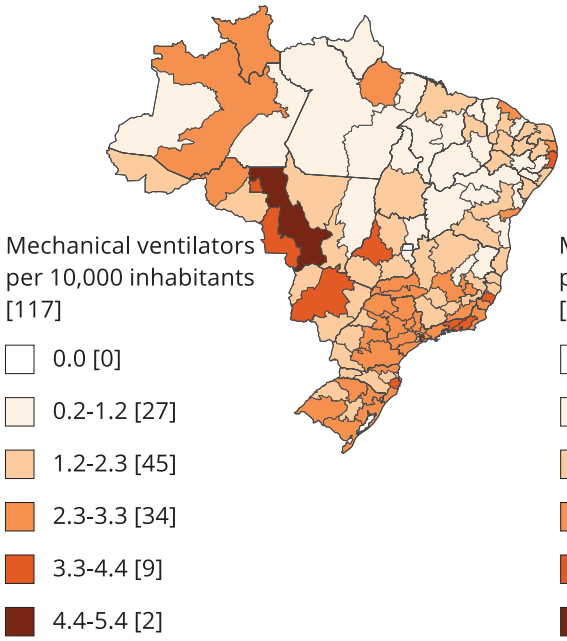
The HPLV collaboration

- Project leader Ian Lazarus, Hannah Newton – STFC, UK.
- WP1 – Brazilian implementation, testing and training – UFRJ, Brazil.
  - Gabriel Antão, Cesar Chagas, Vinicius Côrtes, Kristy Godoy, Fernando Guimarães, Katherine Maslova, Irina Nasteva, Carlos Ortiz, Gabriel Rodrigues.
- WP2 – Regulatory compliance, standards and testing.
  - Tom Clutton-Brock, MD-TEC, UK.
- WP3 – Software and microcontroller.
  - Themis Bowcock, Karol Hennessy – U. of Liverpool, UK.
  - Sofia Fuster Almenar, Jim Bannister, Andrew Hill, Matthew Marshall, Sarah Medley, David Meredith, Benjamin Mummery, Tim Nicholls, Joseph Nobes, Tim Powell, Tiago Sarmento – STFC.
- WP4 – Engineering and prototypes.
  - Phil Allport, Karl Dearn, James Glover, Amir Hajiyavand, Juergen Thomas – U. of Birmingham, UK.
- WP5 – Knowledge transfer.
  - Phil Carvil – STFC, Amanda D. Fernandez, Ben Fritsch – CERN.
  - Jan Buytaert, Paula Collins – HEV / CERN.

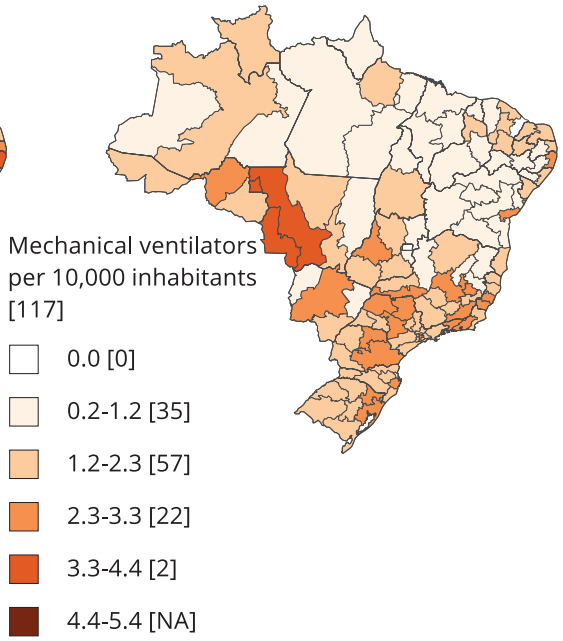
Brazilian clinical conditions

- Clinical conditions vary locally, however the regulations follow the international standards.
  - Gas and electric connections, O_2 consumption, gas pressure.
- Distribution of ICU beds and ventilators is very uneven, with shortages in many regions.
  - Especially in regions of difficult access, where there are few hospitals and ICUs.

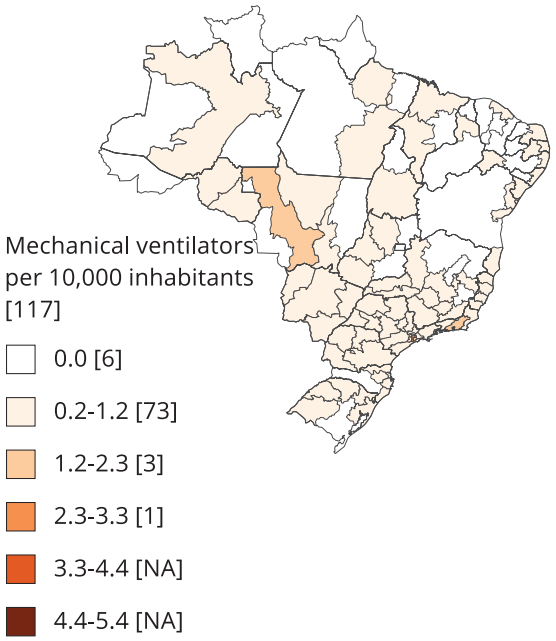
1g) Mechanical ventilators (macro-regions) – Total



1h) Mechanical ventilators (macro-regions) – SUS

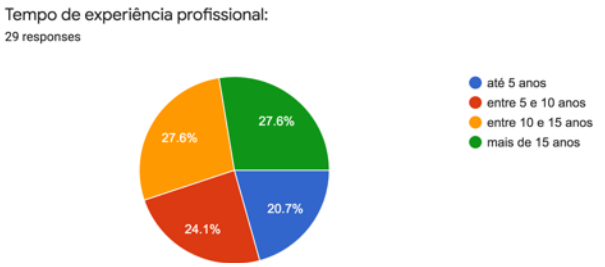


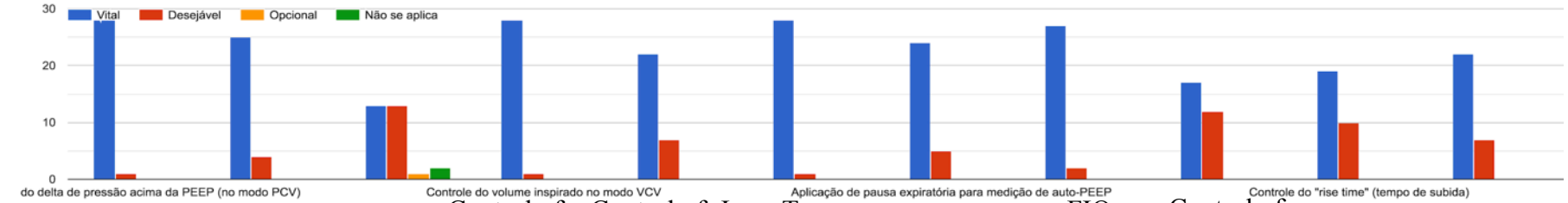
1i) Mechanical ventilators (macro-regions) – Private



K. Noronha et. al., https://doi.org/10.1590/0102-311X00115320

Brazilian end-user needs

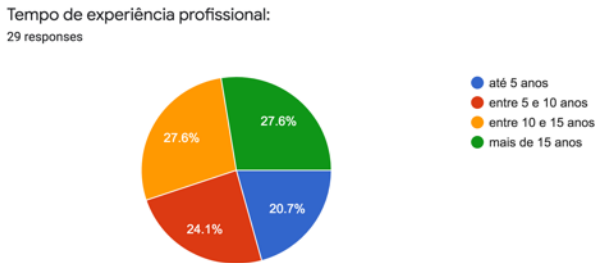


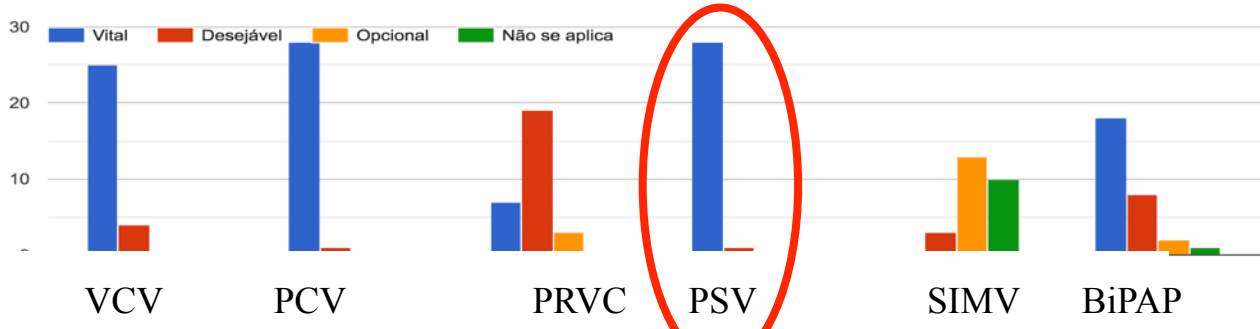


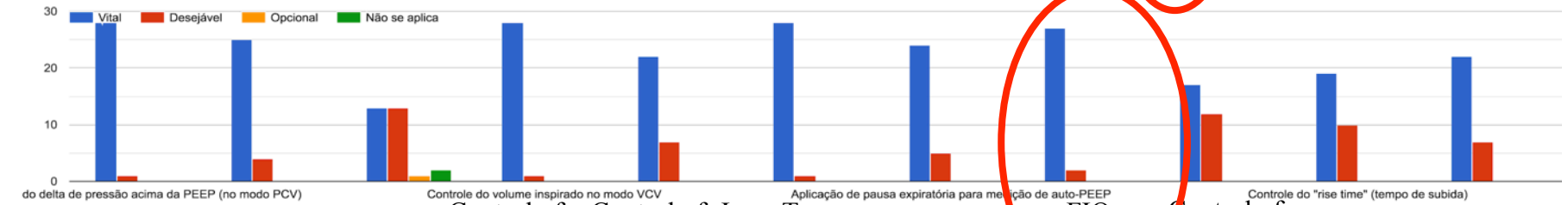
Control of ΔP above PEEP | Tinsp primary variable | I:E primary | Control of Vinsp | Control of insp. flow | Insp. Tpause for Pplateau | Exp. Tpause for auto-PEEP | FIO_2 21-100% | Control of Tpause | Control of rise time | Control of PSV cycling off

- Produced and analysed a survey of 29 Brazilian experienced intensive-care therapists on ventilator use and essential / desirable / optional functionality:
  - Many of the functions, modes and characteristics are already implemented in HEV.
  - Most of the remaining functions can be implemented in software/firmware.
  - All requested monitored parameters and alarms are implemented.
  - Good and intuitive user interface, and keeping historical log of the patient are requested.
  - Oxygen consumption should not be very high.
  - Battery autonomy of 2 hours pointed out as vital – choice of new battery in HPLV.

Brazilian end-user needs



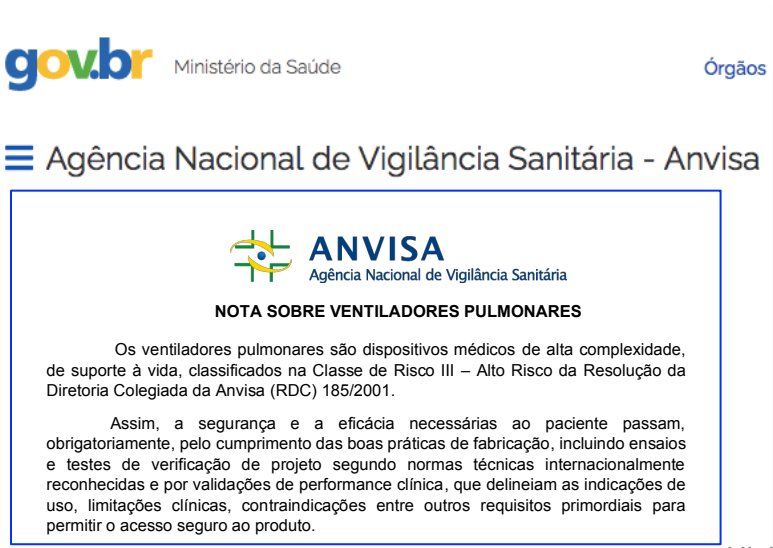




- Produced and analysed a survey of 29 Brazilian experienced intensive-care therapists on ventilator use and essential / desirable / optional functionality:
  - In agreement with medical experts worldwide about the importance of high-quality ventilation, with reliable delivery of high-flow pressure controlled breaths, measurement of the delivered volume, precise synchronisation with the patient breathing, and control of the oxygen mixture of the delivered breaths.

Brazilian regulations

- Brazilian agency ANVISA (National Agency for Sanitary Monitoring) regulates the registration of any medical devices to be employed in the country.
  - Signatory of the International Medical Device Regulators Forum (IMDRF).
  - Also adopts the Medical Device Single Audit Program (MDSAP).
  - Most ANVISA resolutions follow the internationally adopted ones.
- After initially implementing emergency procedures for regularisation of devices during COVID-19, ANVISA later went back to its full requirements.
  - Note on pulmonary ventilators (May 2020).
  - Guide of Medical Device Cybersecurity (Sep 2020, based on IMDRF).
  - Technical Note on Software for Health products (2012).
  - ABNT PR 1003:2020 – Recommended practice on Pulmonary ventilators for critical care.


gov.br Ministério da Saúde Órgãos

Agência Nacional de Vigilância Sanitária - Anvisa

ANVISA
Agência Nacional de Vigilância Sanitária

NOTA SOBRE VENTILADORES PULMONARES

Os ventiladores pulmonares são dispositivos médicos de alta complexidade, de suporte à vida, classificados na Classe de Risco III – Alto Risco da Resolução da Diretoria Colegiada da Anvisa (RDC) 185/2001.

Assim, a segurança e a eficácia necessárias ao paciente passam, obrigatoriamente, pelo cumprimento das boas práticas de fabricação, incluindo ensaios e testes de verificação de projeto segundo normas técnicas internacionalmente reconhecidas e por validações de performance clínica, que delineiam as indicações de uso, limitações clínicas, contraindicações entre outros requisitos primordiais para permitir o acesso seguro ao produto.


Principles and practices for medical device cybersecurity

Guide nº 38/2020 – version 1

ANVISA

National Agency for Sanitary Monitoring - Anvisa

2020


ANVISA

National Agency for Sanitary Monitoring – ANVISA
General Management of Health Products Technology – GGTPS
Equipment Technology Management – GQUIP

TECHNICAL NOTE N° 04/2012/GQUIP/GGTPS/ANVISA

1. **Target:** To serve as a guide for companies in the health products sector for health software.

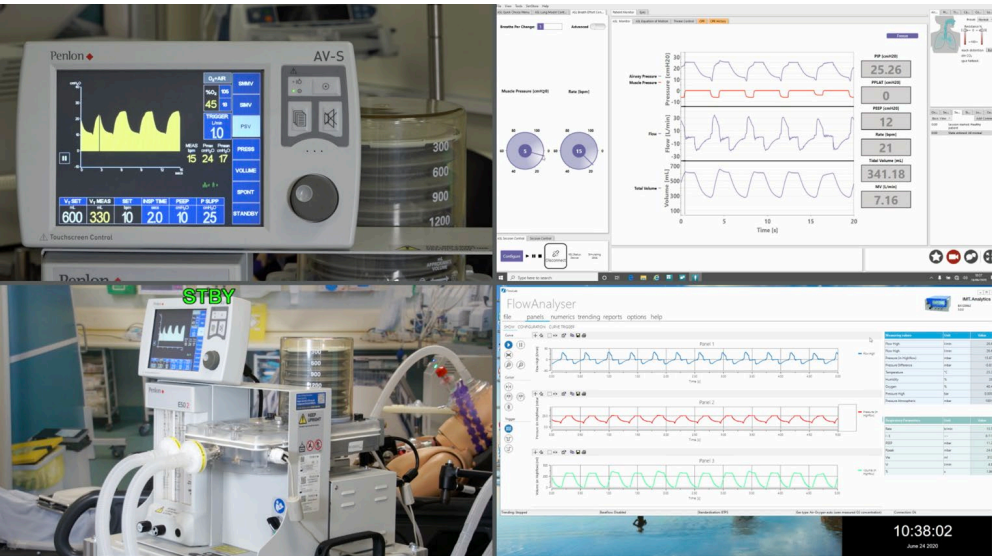
1. Purpose

Considering the great demand in software inquiries and the lack of a specific regulation, this technical note was generated to clarify the normative application of health surveillance to software understood as health products.

Regulatory compliance

- All development followed clinical advice on regulatory aspects and applicable standards.
  - List of Essential Requirements based on identified needs and norms.
  - ISO 80601-2-12:2020, Medical electrical equipment — Part 2-12: Particular requirements for basic safety and essential performance of critical care ventilators.
  - RMVS / WHO and Brazilian requirements.
- Continuous feedback to engineering and software development, as well as documentation.
- Clinical and regulatory advice guided the in depth Risk Analysis process and tests.
  - ISO 14971:2019, Application of risk management to medical devices.

MD-TEC ventilator testing facility



Risk Traceability Matrix

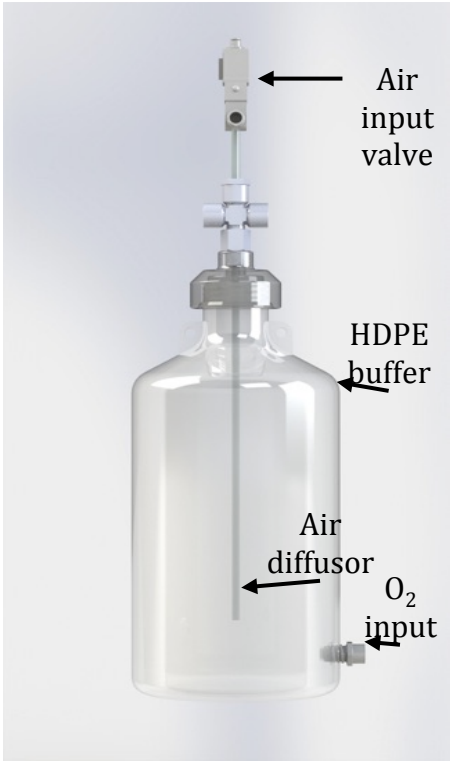
IDENTIFICATION OF		RISK ANALYSIS							RISK EVALUATION		
Risk ID	User Requirement	Hazard	Hazardous Situation(s)	Harm	Pre-existing Control Measures	Existing Alarms	Frequency (F)	Severity (S)	Risk Level	Next Step	Reasoning for 'Mediu Risk Level Next Step
SW1	Accidental operation of on-off switch must be prevented	Unexpected shutdown of ventilator	Patient stops receiving breathing support.	Hypoxia / Hypercarbia	2-second press of button + confirmation message required before off action initiated. Separate on/off buttons.	N/A	Remote	Catastrophic/Fatal	High	Proceed to Risk Control	N/A
SW2	The ventilator shall include a means for the healthcare professional operator to confirm the ventilation-mode and settings: during start-up and when changing mode.	Incorrect pressure/volume etc applied to patient	Inadequate / excessive ventilation for patient	Hypoxia / Hypercarbia / barotrauma	Confirmation required to apply any changes to settings. Pop-up to confirm the change (what you are changing from to what are you changing to -> confirm).	Yes	Improbable	Catastrophic/Fatal	Medium	Treat as Residual Risk	Confirmation ensures no accidental changes of mode and settings.
SW3	Device subsystems must allow operator input to change values for settings	Incorrect pressure/volume etc applied to patient	Inadequate / excessive ventilation for patient	Hypoxia / Hypercarbia / barotrauma	Robust software and hardware to be verified through testing.	Yes	Remote	Catastrophic/Fatal	High	Proceed to Risk Control	N/A
SW4	The ventilator shall have means to indicate visually the cumulative hours of operation of the ventilator, either manually or by operator action	Unexpected shutdown of ventilator	Patient stops receiving breathing support.	Hypoxia / Hypercarbia	No pre-existing control measures	No	Improbable	Catastrophic/Fatal	Medium	Proceed to Risk Control	Features need to be implemented in the U for this requirement.
SW5	The ventilator should also have means to indicate visually: the time since the last preventive maintenance; or the time until the next recommended preventive maintenance.	Unexpected shutdown of ventilator	Patient stops receiving breathing support.	Hypoxia / Hypercarbia	No pre-existing control measures	No	Improbable	Catastrophic/Fatal	Medium	Proceed to Risk Control	Features need to be implemented in the U for this requirement.
SW6	Testing of alarm volume by healthcare professional operator at start up	Incorrect pressure/volume etc applied to patient	Inadequate / excessive ventilation for patient	Hypoxia / Hypercarbia / barotrauma	No pre-existing control measures	N/A	Improbable	Catastrophic/Fatal	Medium	Proceed to Risk Control	Features need to be implemented in the U for this requirement.

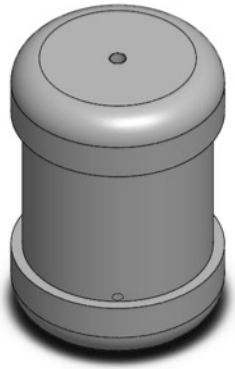
Engineering and design

- Design was re-engineered for manufacturing.
  - Repackaging of prototype to reduce size and weight.
  - Ergonomic casing design with smooth corners and edges.
  - Separate electronic and pneumatic sections.
  - Relocation of the outlet exhale line and inhale guarantee allowing better accessibility.
  - Integrated touch screen and robust handle.

HPLV mechanical components

- Biocompatibility of choice of materials in compliance with regulations.
  - All materials in contact with gases are oxygen-, biocompatible and non-toxic.
- Use of medical-grade pneumatic parts and valves.
  - When not immediately available, an equivalent valve was used that can be certified.
- Alternative designs of air buffer to reduce weight and cost.
  - High-density polyethylene, lighter than 1 kg and several times cheaper.
- An alternative Bill of Material with locally sourced components in Brazil.



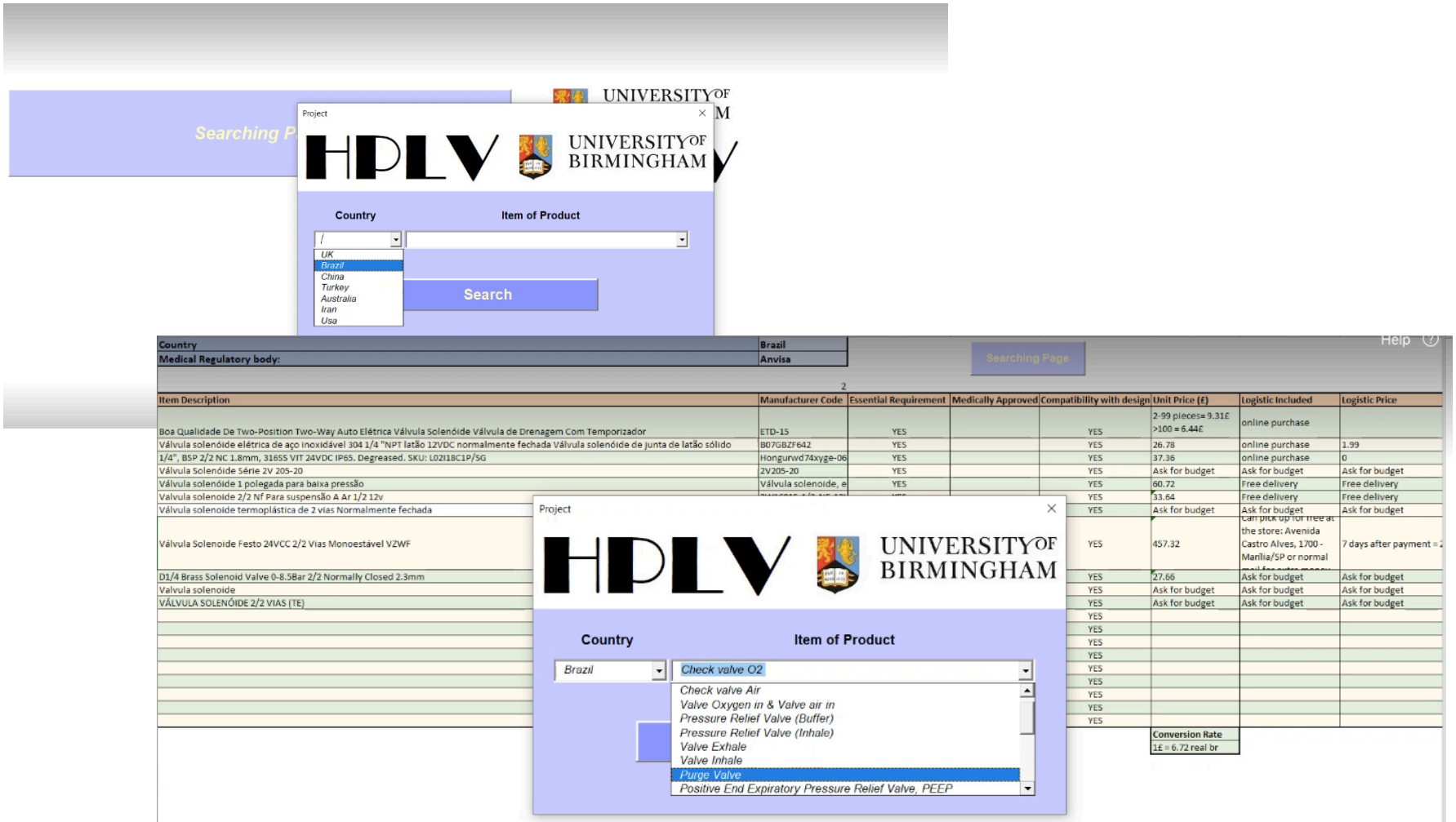


High Density Polyethylene
Dimensions
Ø251.8 x 326.8 [mm]

Polypropylene
Dimensions
Ø180 x 570 [mm]

Supply chain database

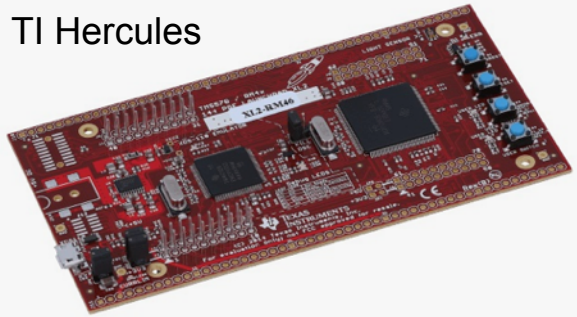
- Software database for sourcing equivalent parts in different regions of the world.
  - Investigated the available suppliers in 7 representative countries.
  - Searchable bill of material with detailed info and links to suppliers.



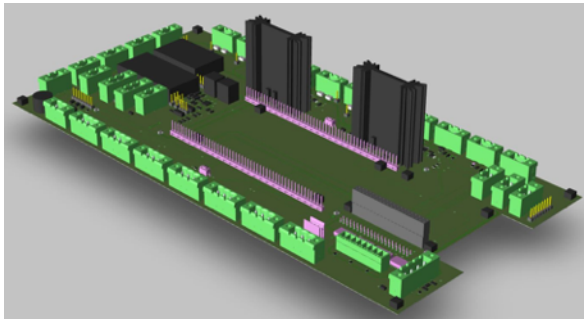
Redesigned electronics

- The electronics were redesigned for medical compatibility, safety and compliance with norms.
  - Microcontroller: safety-critical TI Hercules.
  - Single-board computer: Asus Tinkerboard.
  - PCB motherboard: redesigned for new components.
- Powered via a medical-grade Uninterrupted Power Supply.
  - Onyx UPower Pro-22 with 2 batteries of 90 Wh each.
  - 2 hour autonomy and software access to battery data.

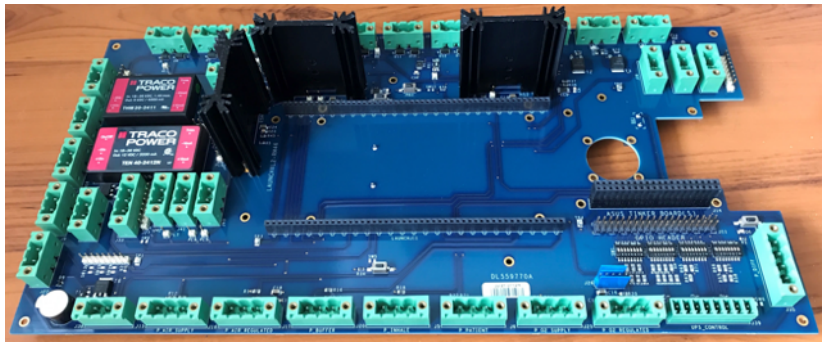
TI Hercules



Asus Tinkerboard



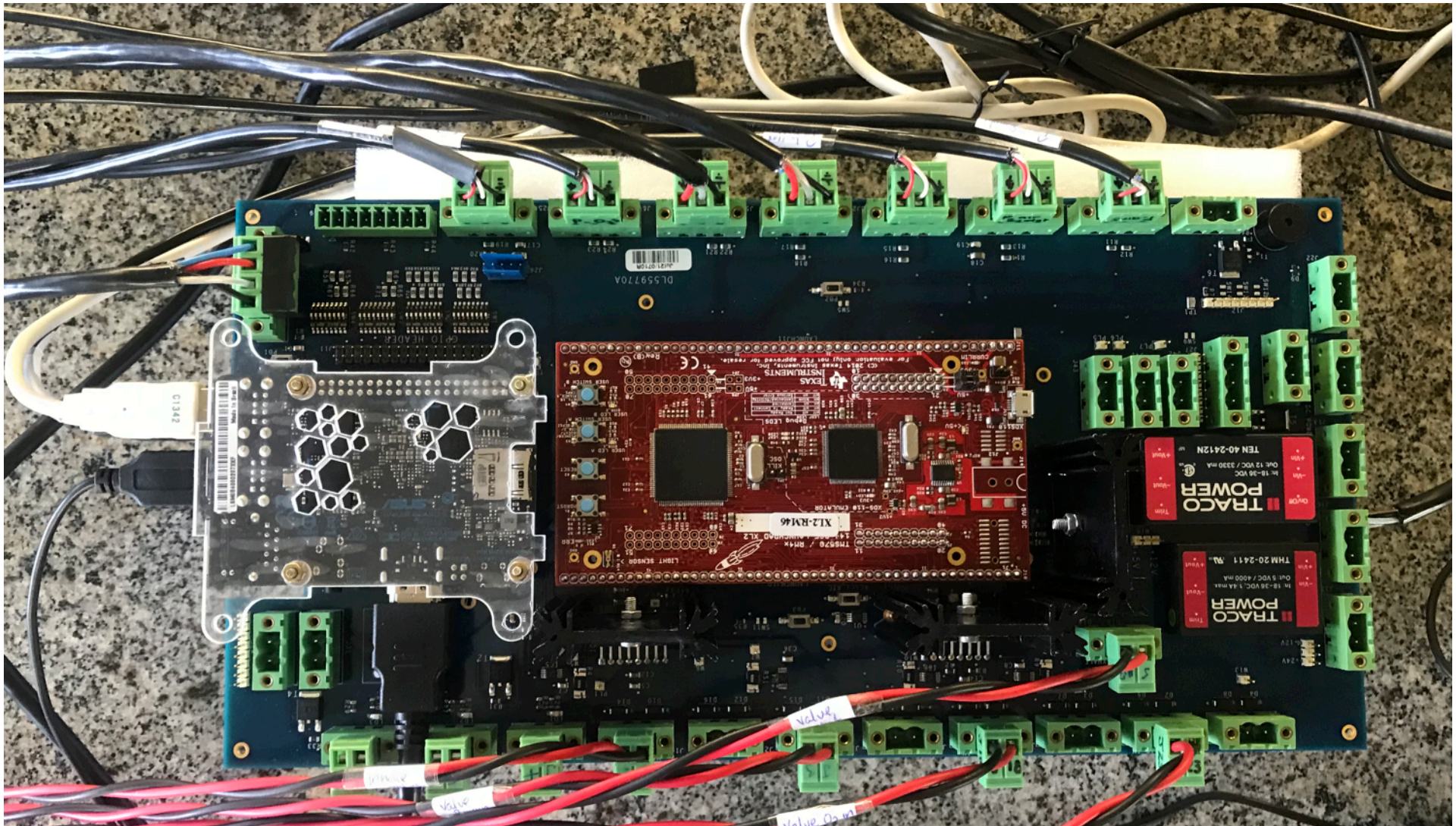
Motherboard



UPS

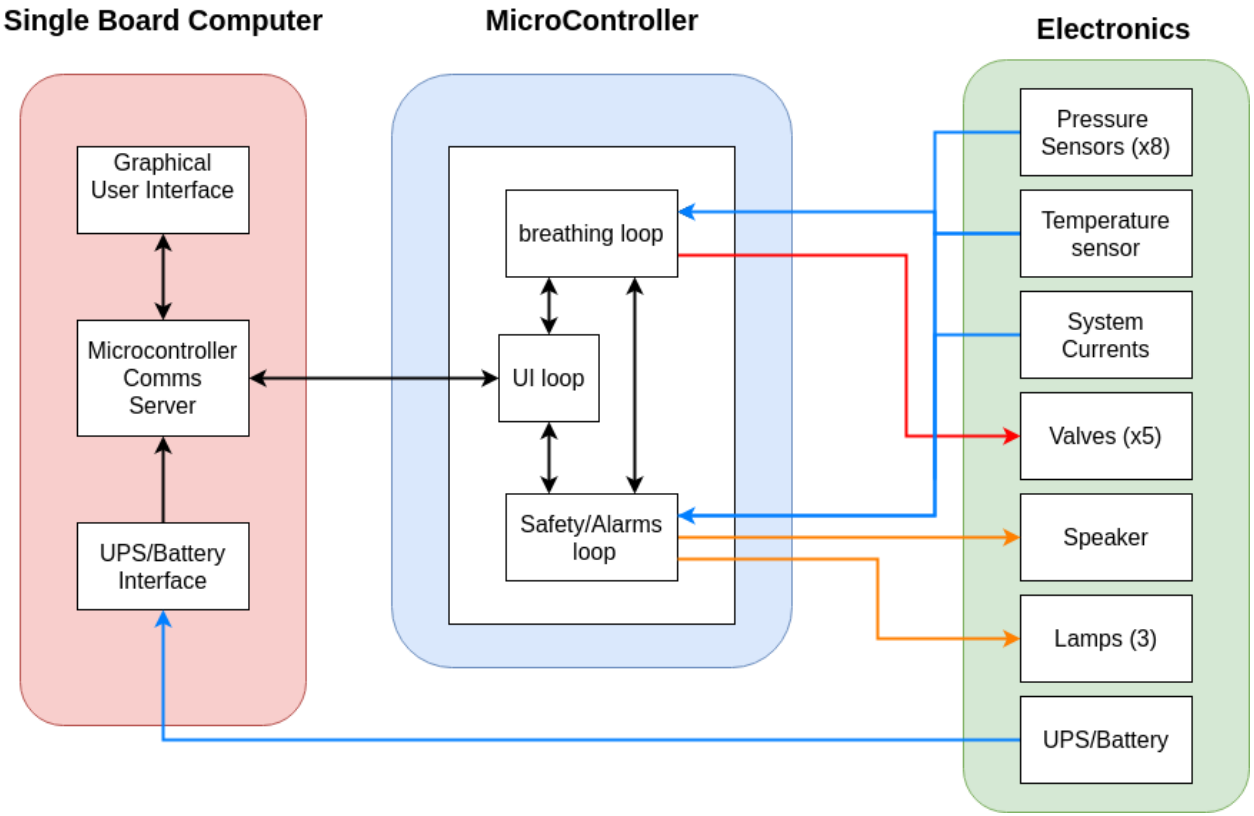
Redesigned electronics

- The electronics were redesigned for medical compatibility and compliance with norms.
  - Microcontroller, Single-board computer, motherboard, medical-grade UPS.



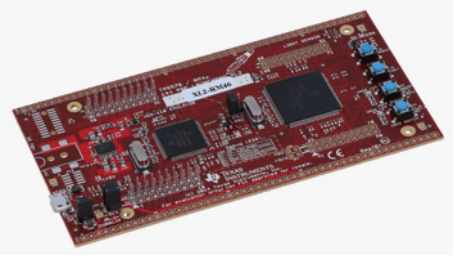
Software

- The software organisation follows that of HEV.
  - The microcontroller controls the operation of valves, monitors sensors, and controls the breathing functions.
  - The single-board computer runs the user interface client and server, connected to a touch screen for receiving input and displaying information.

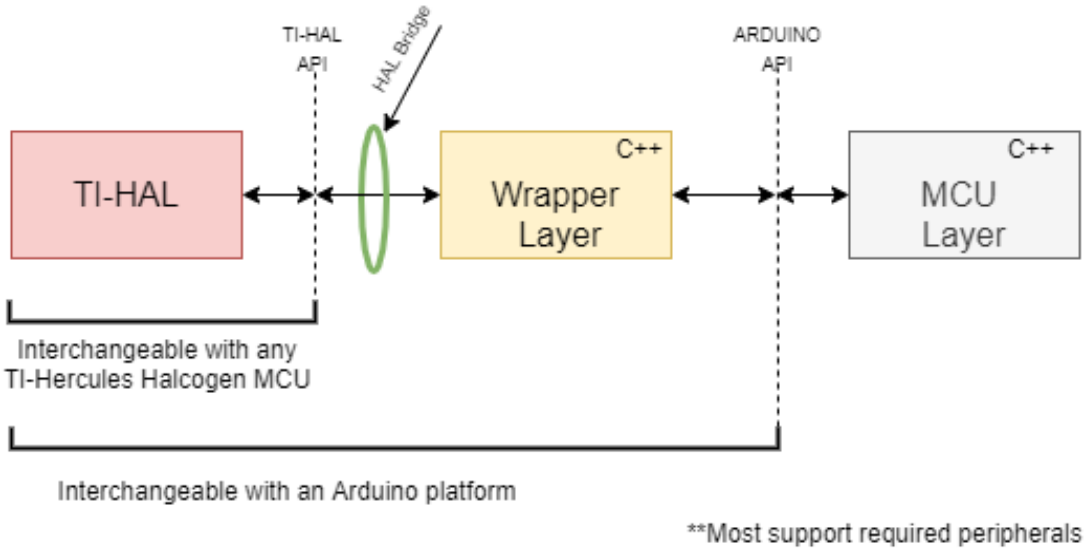


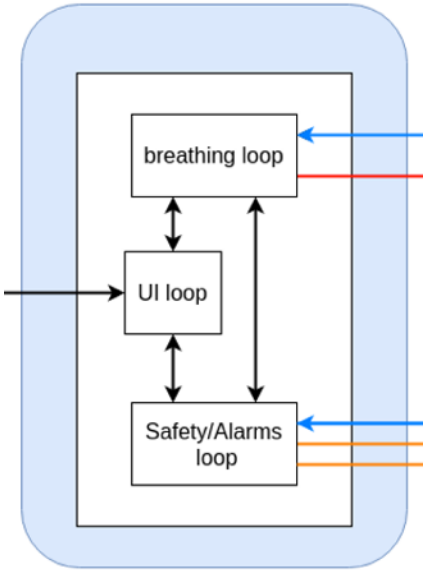
Microcontroller software

- Controls the operation of valves, monitoring of sensors, and the breathing functions.
  - 3 independent loops: breathing, safety/alarms and user interface.
  - Semi-independent final-state machines with exchange of information.
  - Continues cycling even if contact lost with user interface.
- The microcontroller code was ported to the TI Hercules.
  - Safety-grade and triplicate redundancy.
- The code was rewritten and tested to comply with regulations.
  - Modularity: hardware abstraction, wrapper and higher level.



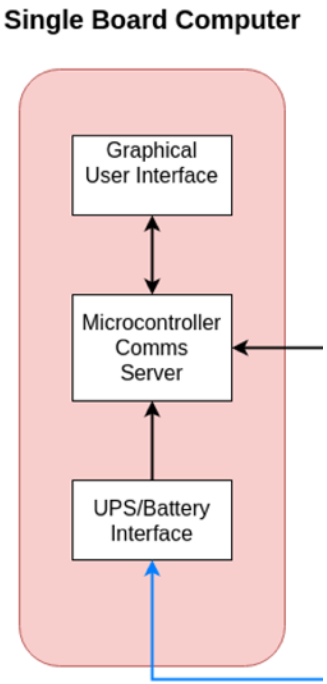
MicroController





User interface software

- The single-board computer runs the user interface client and data server.
  - Connection to a touch screen for display and receiving input.
  - Communication protocol: High-level Data Link Control, certified ISO/IEC 13239:2002.
  - Handling of alarms.
  - Interface to UPS battery for display and alarms.
- Code ported to the Asus Tinkerboard, migrated to Python with Qt library.
- Communications, logic, and layout are largely separate to facilitate development.
- Usability improvements, based on clinical guidance.
- Multi-language capability implementation.

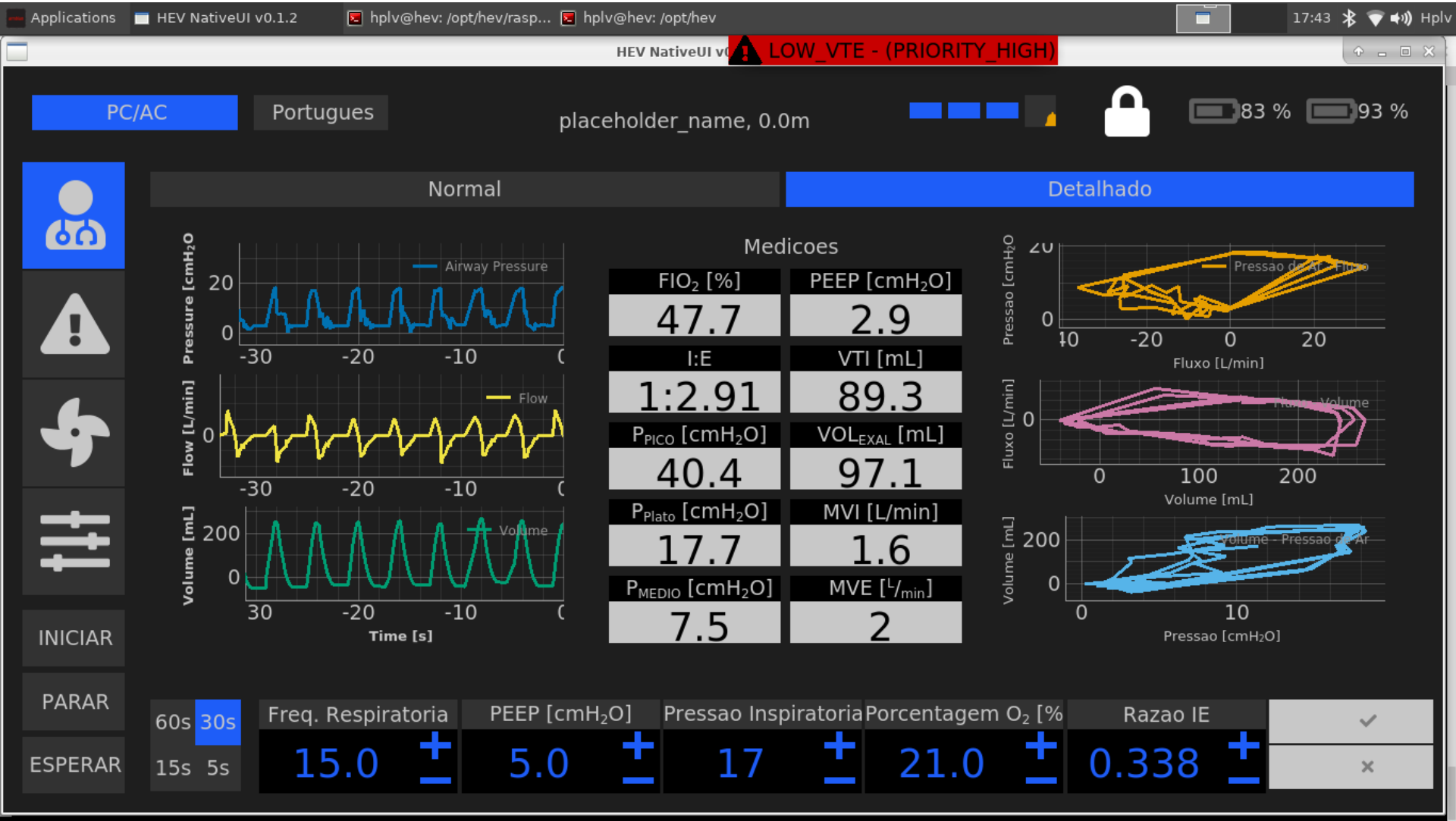


User interface

- User interface in English and Portuguese.
  - Language option as modularity in the code, any language can be added easily.

User interface

- User interface in English and Portuguese.
  - Language option as modularity in the code, any language can be added easily.

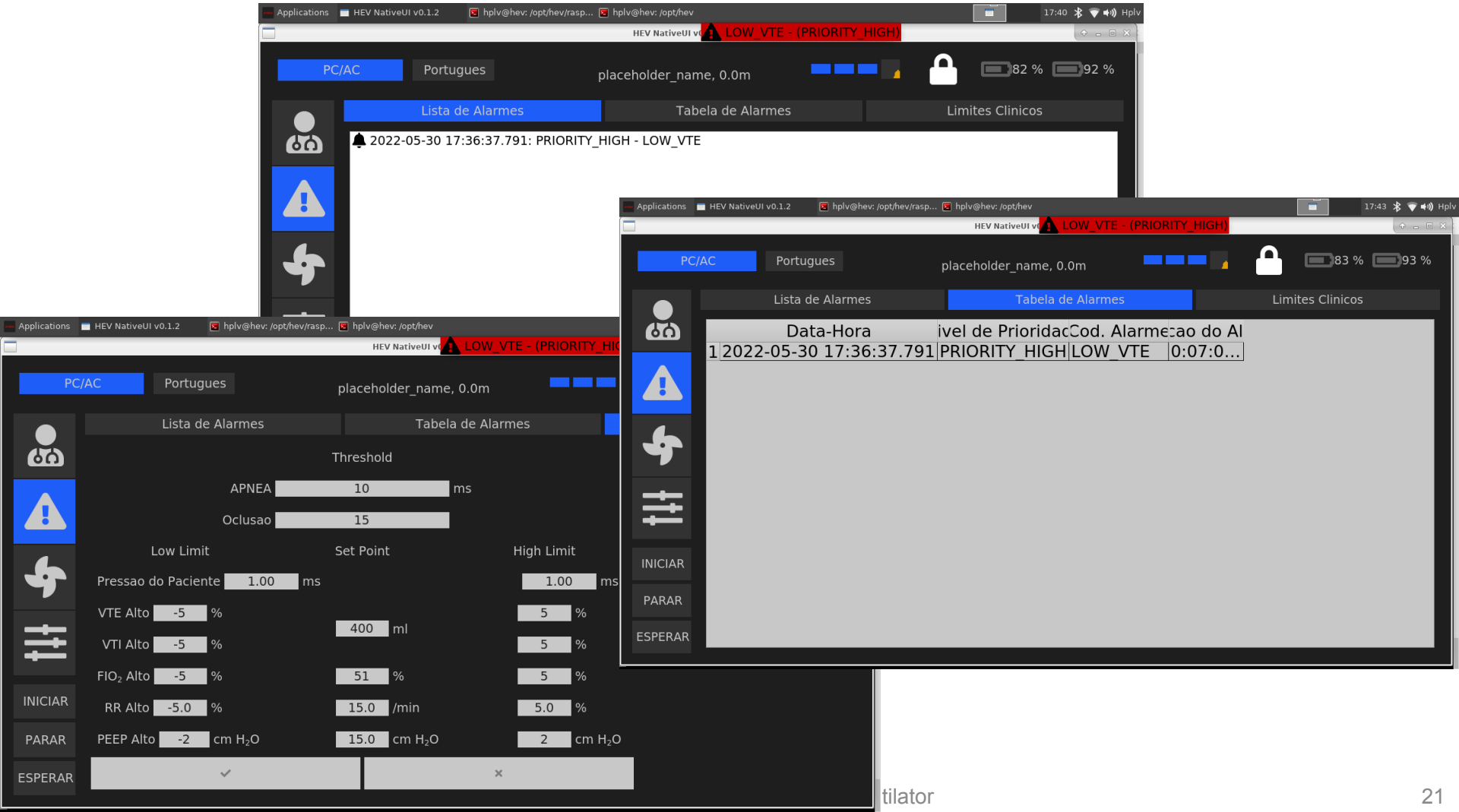


User interface

- User interface in English and Portuguese.
  - Ventilation mode and parameter settings, patient information.

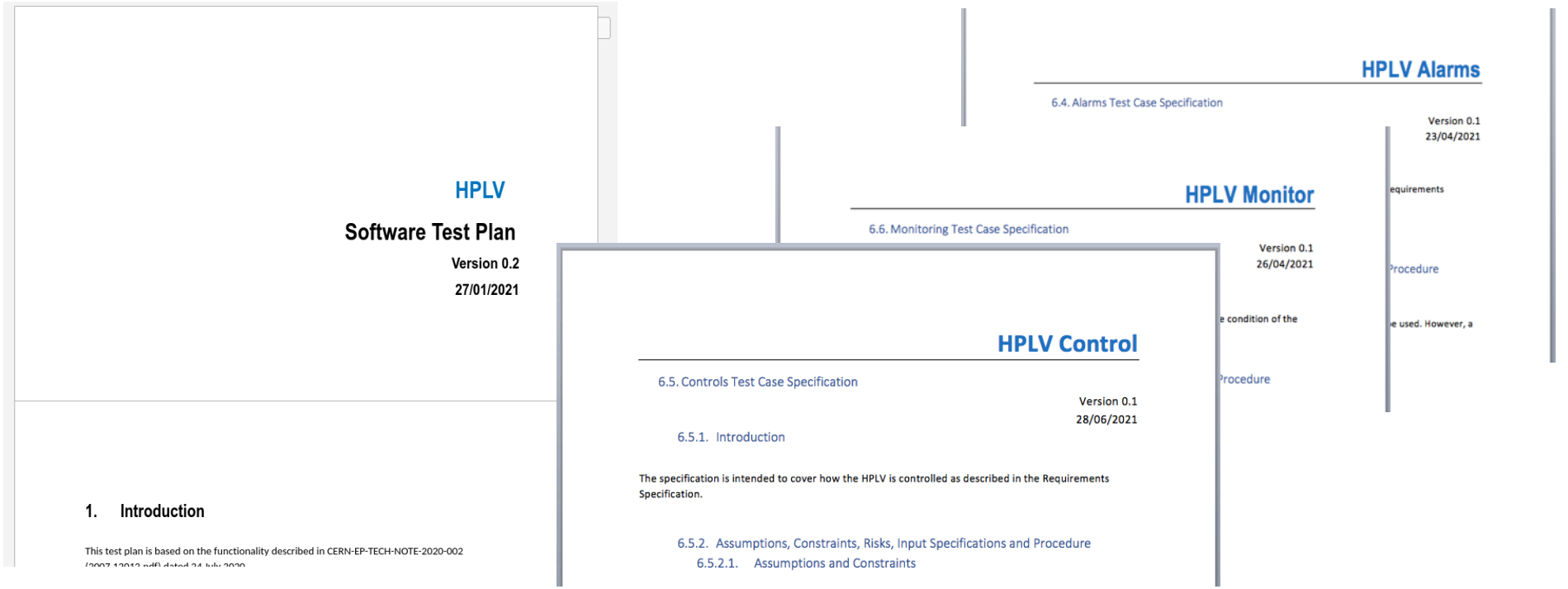
User interface

- User interface in English and Portuguese.
  - Alarms list, table and limit settings.



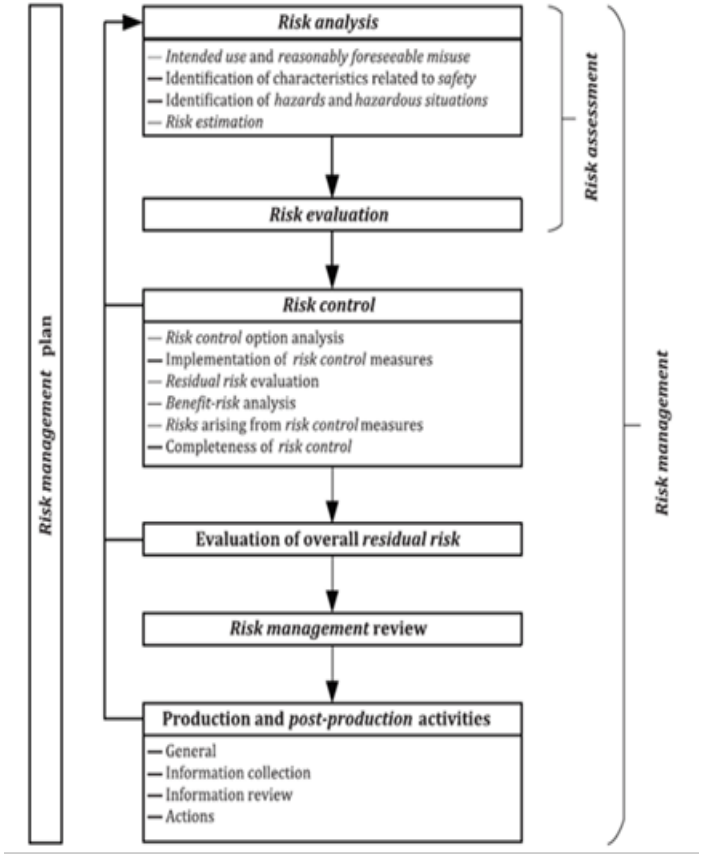
Software tests

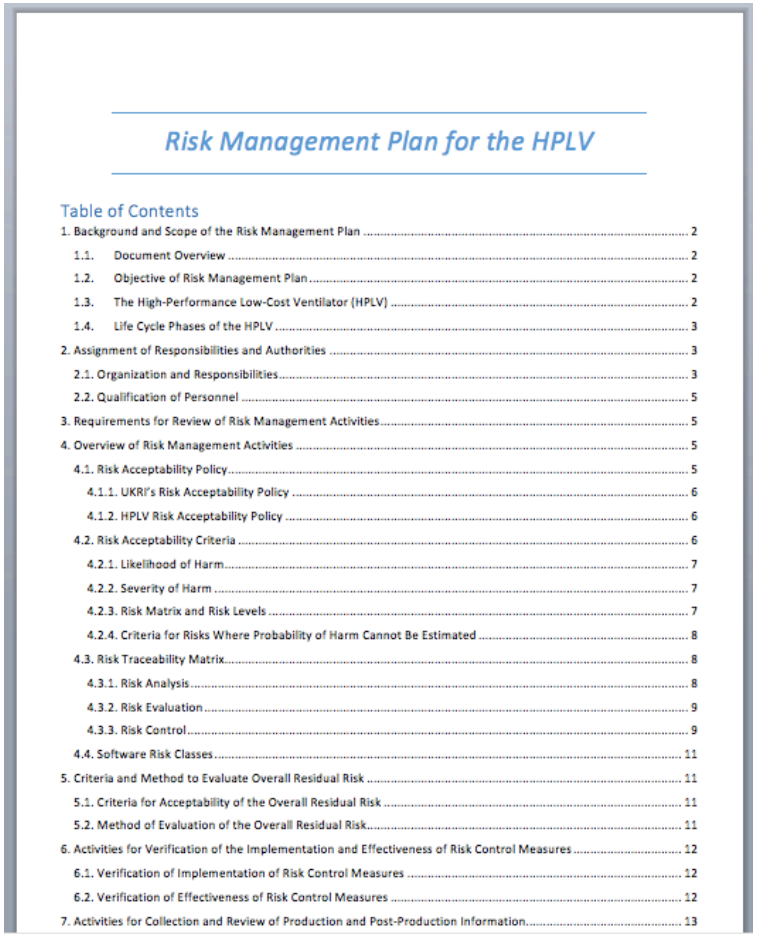
- Software testing implemented alongside the development following ISO/IEC: 62304.
  - Software Test Plan based on IEEE 829-2008 (Software and system test documentation) to cover compliance with BS EN 62304 (Medical device software).
  - 3 types of tests: Software unit implementation and verification, Software integration testing, and Software system testing.
  - 3 Test Case Specifications: HPLV Alarms, HPLV Control, and HPLV Monitor.
  - Software of Unknown Provenance (SOUP) anomaly list evaluation, IEC 62304:2006.



Risk analysis

- A comprehensive risk analysis was performed based on the HPLV Essential Requirements.
  - Literature review of the standards for risk analysis for medical devices.
  - Risk Management Plan following ISO 14971:2019, ISO/TR 24971:2020, IEC 62304:2006 and IEC 62366-1.



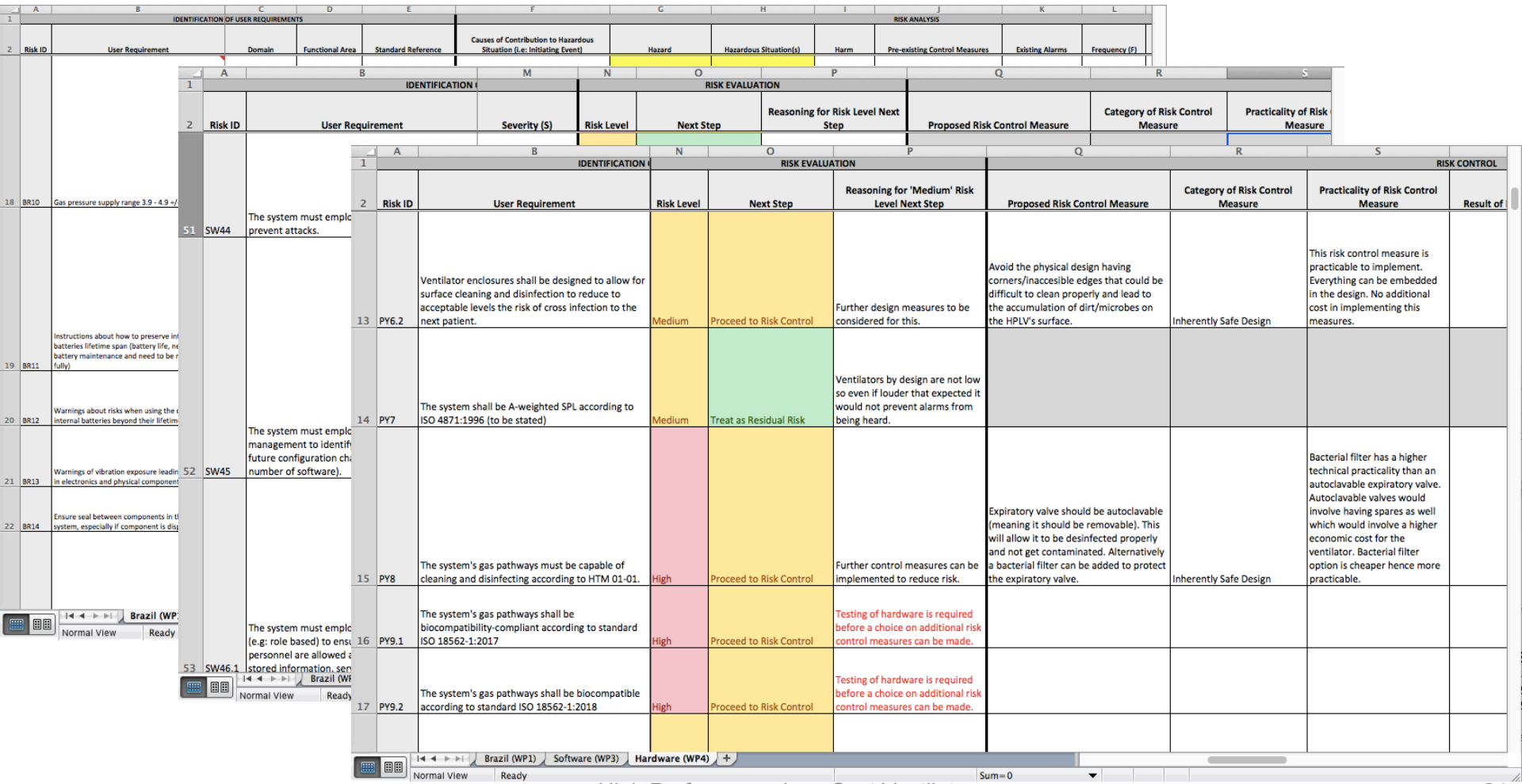


Risk Management Plan for the HPLV

Table of Contents

Risk analysis

- A comprehensive risk analysis was performed based on the HPLV Essential Requirements.
  - Risk Traceability Matrix divided by hardware, software, and Brazilian implementation.
  - Risk Analysis, Risk Evaluation, Risk Control and Testing Results.



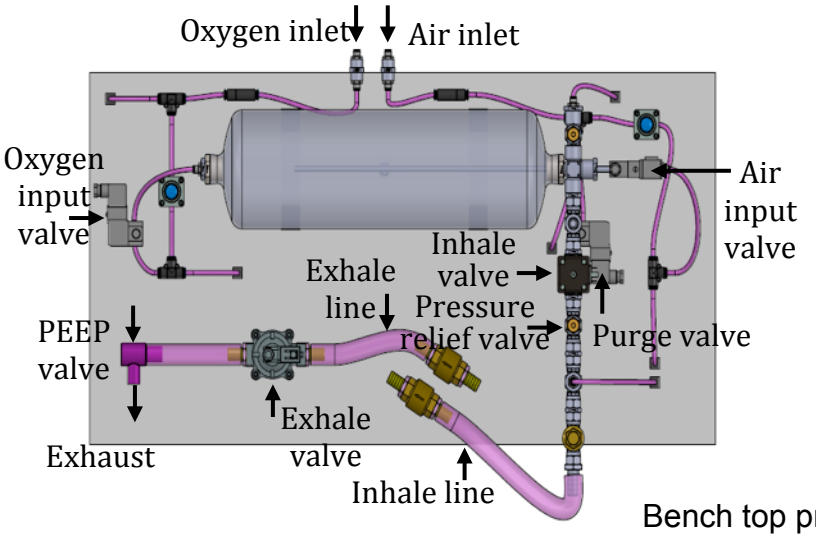
Risk ID	User Requirement	Domain	Functional Area	Standard Reference	Causes of Contribution to Hazardous Situation (i.e: Initiating Event)	Hazard	Hazardous Situation(s)	Harm	Pre-existing Control Measures	Existing Alarms	Frequency (F)
BR10	Gas pressure supply range 3.9 - 4.9 +/-										
BR11	Instructions about how to preserve int batteries lifetime span (battery life, ne battery maintenance and need to be r fully)										
BR12	Warnings about risks when using the c internal batteries beyond their lifetim										
BR13	Warnings of vibration exposure leadin in electronics and physical component										
BR14	Ensure seal between components in t system, especially if component is disp										

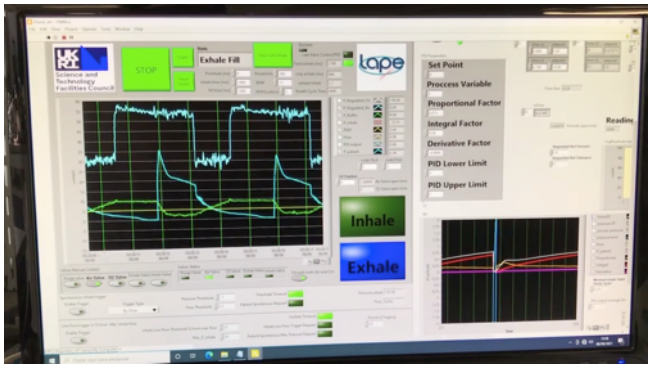
Risk ID	User Requirement	Severity (S)	Risk Level	Next Step	Reasoning for Risk Level Next Step	Proposed Risk Control Measure	Category of Risk Control Measure	Practicality of Risk Measure
SW44	The system must emplo prevent attacks.							
SW45	The system must emplo management to identif future configuration cha number of software).							
SW46.1	The system must emplo (e.g: role based) to ensu personnel are allowed a stored information, ser							

Risk ID	User Requirement	Risk Level	Next Step	Reasoning for 'Medium' Risk Level Next Step	Proposed Risk Control Measure	Category of Risk Control Measure	Practicality of Risk Control Measure	Result of
PY6.2	Ventilator enclosures shall be designed to allow for surface cleaning and disinfection to reduce to acceptable levels the risk of cross infection to the next patient.	Medium	Proceed to Risk Control	Further design measures to be considered for this.	Avoid the physical design having corners/inaccesible edges that could be difficult to clean properly and lead to the accumulation of dirt/microbes on the HPLV's surface.	Inherently Safe Design	This risk control measure is practicable to implement. Everything can be embedded in the design. No additional cost in implementing this measures.	
PY7	The system shall be A-weighted SPL according to ISO 4871:1996 (to be stated)	Medium	Treat as Residual Risk	Ventilators by design are not low so even if louder that expected it would not prevent alarms from being heard.				
PY8	The system's gas pathways must be capable of cleaning and disinfecting according to HTM 01-01.	High	Proceed to Risk Control	Further control measures can be implemented to reduce risk.	Expiratory valve should be autoclavable (meaning it should be removable). This will allow it to be desinfected properly and not get contaminated. Alternatively a bacterial filter can be added to protect the expiratory valve.	Inherently Safe Design	Bacterial filter has a higher technical practicality than an autoclavable expiratory valve. Autoclavable valves would involve having spares as well which would involve a higher economic cost for the ventilator. Bacterial filter option is cheaper hence more practicable.	
PY9.1	The system's gas pathways shall be biocompatibility-compliant according to standard ISO 18562-1:2017	High	Proceed to Risk Control	Testing of hardware is required before a choice on additional risk control measures can be made.				
PY9.2	The system's gas pathways shall be biocompatible according to standard ISO 18562-1:2018	High	Proceed to Risk Control	Testing of hardware is required before a choice on additional risk control measures can be made.				

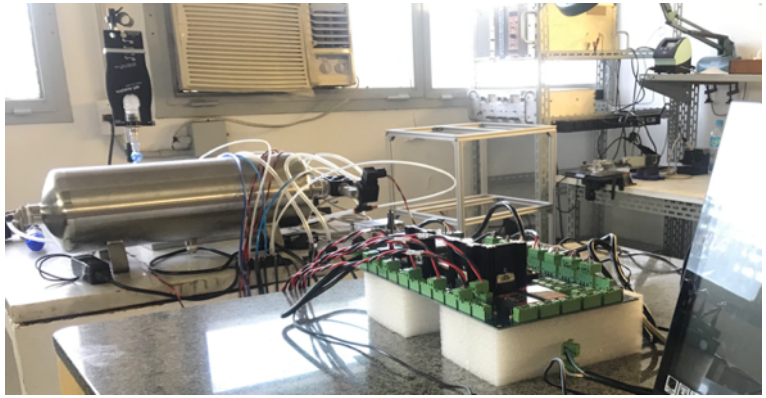
Prototypes

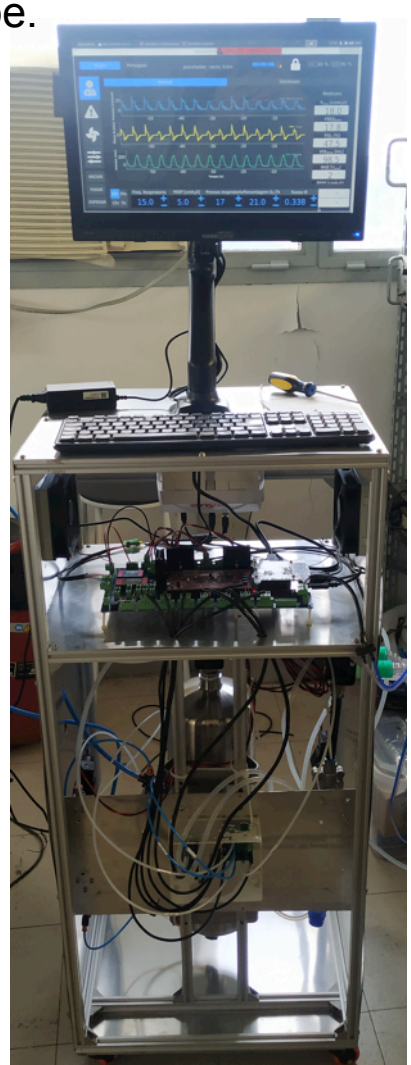
- Prototypes were developed in parallel in Birmingham and Rio de Janeiro.
  - Bench top prototype and aesthetic prototype in Birmingham.
  - Bench top prototype in Brazil, later integrated into a full prototype.





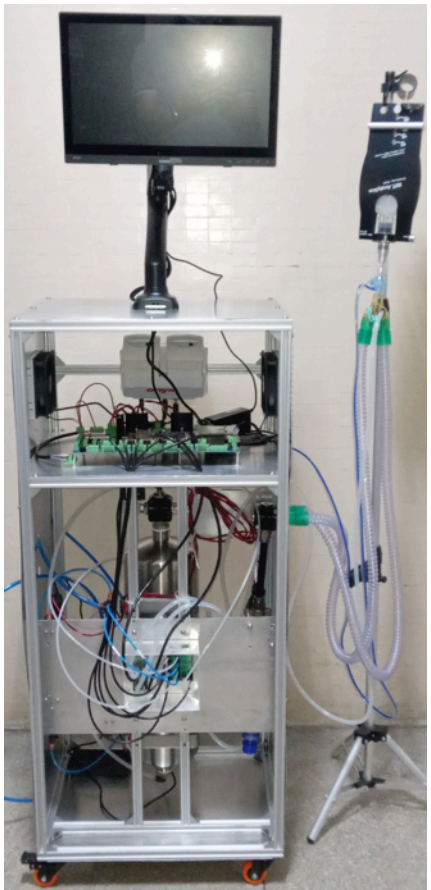
Bench top prototype in Rio de Janeiro

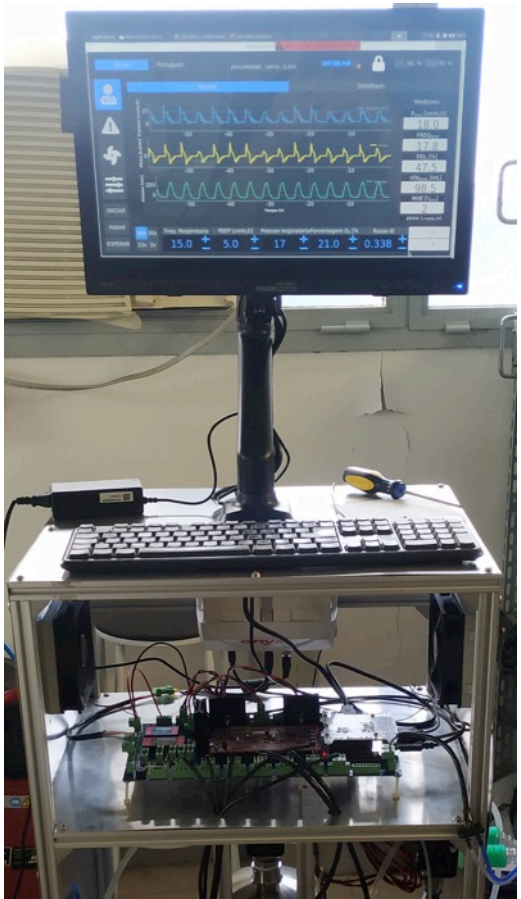




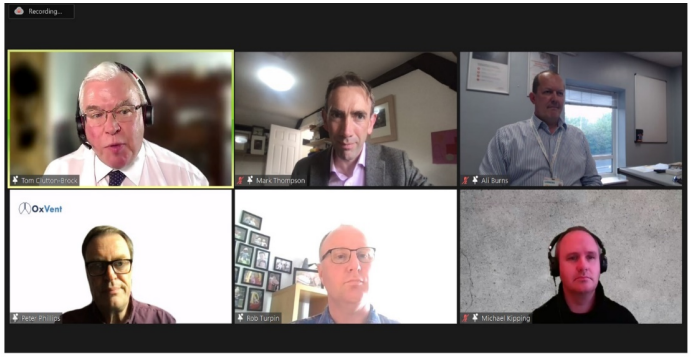
Prototype integration and tests

- The integration of the mechanics, electronics and software was done on the Rio prototype.
  - Hardware testing and improvements of electronic board.
- Tests of the prototype operation and functionalities with a SmartLung test lung.
  - Debugging, tests of functions and optimisation of microcontroller and UI software.
- Next steps: tests with a ventilator analyser, training materials for users (in Portuguese).





HPLV engagement



Ventilator Challenge – 1 Year on | 11th May 2021

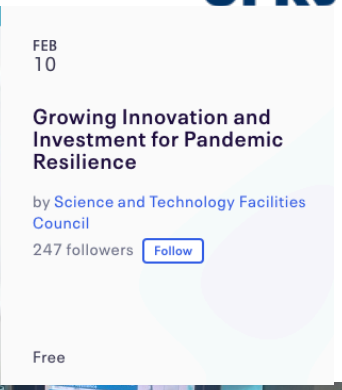
technology

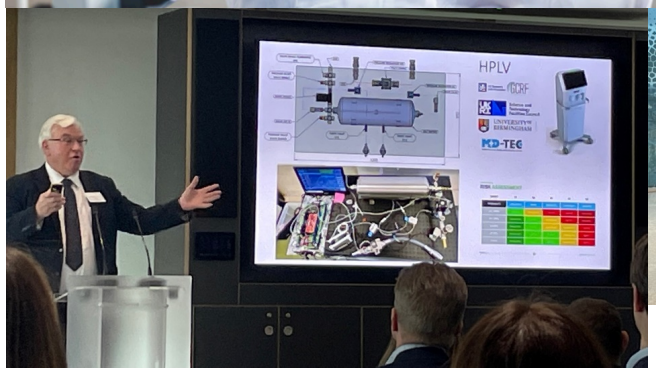
Science and Technology Facilities Council

Panellists:

- Ali Burns, Managing Director Siemens Healthcare Diagnostics Manufacturing Ltd & Member of Executive Leadership Team VCUK
- Professor Mark Thompson, Director, Oxvent
- Dr Michael Kipping, Innovate UK
- Peter Phillips, CEO, OxVent
- Rob Turpin, Head of Sector (Healthcare) BSI Knowledge Solutions
- **Chair:** Professor Tom Clutton-Brock, Director, Medical Devices Testing and Evaluation Centre

Up Next @ 15:10 BST Lessons Learned – How can we improve our responsiveness to future rapid response challenges in healthcare technology?

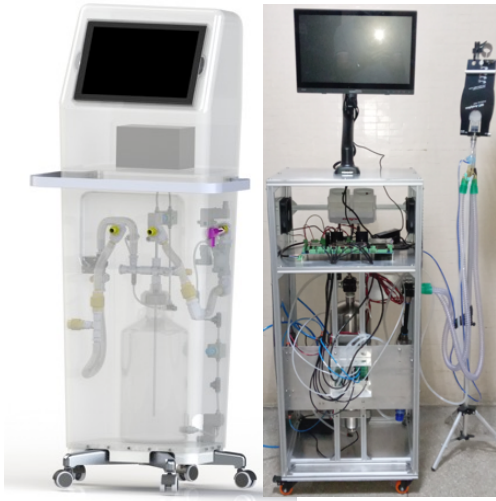




- CERN-STFC working group on Knowledge Transfer advises on IP considerations.
  - Organised online event The Ventilator Challenge - One year on (11 May 2021), bringing together learnings from other projects including the HEV and HPLV.
  - Commissioned market study for Indian Market on Ventilator Need in 2021.
  - Hosted large scale event Growing Innovation and Investment for Pandemic Resilience with partners in the UK (10-11 Feb 2022) – showcasing HPLV to over 100 attendees.
- Will continue to offer license opportunities for HEV and from HPLV developments.

HPLV results summary

- HEV and HPLV apply technology developed in fundamental science research to an innovative medical application.
- Design led by user requirements and in compliance with regulations.
- Focus on safety, functionality and performance.
- A re-engineered HPLV ventilator that meets end-user requirements in Brazil and international regulatory norms for medical devices.
  - Medical-grade components and electronics.
  - Software rewritten and tested according to standards.
  - User interface with multi-language capability.
- A pre-regulatory documentation pack / technical file:
  - Bill of material and supply chain database for different regions.
  - Technical drawings of components and assembly.
  - In depth Risk Analysis documentation.
  - Software Technical File with description, test results and plans.



These technological developments and documentation can enable a company to rapidly take the device through regulatory approval to manufacture and deployment.

Interested in using one of these technologies?

HEV is available for licensing from CERN

HPLV will be made available soon

For more information please contact:

kt.medicalapplications@cern.ch