Cover Page	
Study Title	EASiVENT *Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU subjects*.
Study NCT number	NCT04400643
Document	Clinical Investigation Plan
Document version and Date	2.0 02 October 2020

Clinical Investigation Protocol EASiVENT

Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU subjects

Study Type:	Interventional with low risk, Medical Device (MD)
Study Categorization:	Pivotal (US), PMCF (EFTA)
Study Registration:	ClinicalTrials.gov Identifier: NCT04400643
Sponsor: **US Sponsor (local):**	Hamilton Medical AG, Via Crusch 8, CH 7402 Bonaduz, Switzerland Hamilton Medical Inc., 4655 Aircenter Circle Reno NV 89502 USA
Principal Investigator:	**Omitted**
Investigational Product:	INTELLiVENT-ASV
Protocol Version and Date:	Version 2.0 – 02 October 2020

CONFIDENTIAL

Signature Page(s)

Clinical Study Document Approval Form	
Study Title	EASiVENT *Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU subjects.*
Study number	NCT04400643
Document version and Date	2.0 02 October 2020
The Sponsor approved the protocol version 2.0 dated 02 October 2020, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki (2013), ICH-GCP guidelines and ISO 14155:2020 standard and the local legally applicable requirements.	

Author Name:	**Role or Title:**
Signature	Signature Date (DD/MMM/YYYY)
Author Name:	**Role or Title:**
Signature	Signature Date (DD/MMM/YYYY)
Approver Name:	**Role or Title:**
Signature	Signature Date (DD/MMM/YYYY)

Principal Investigator

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki (2013), ICH-GCP guidelines or ISO 14155: 2020 norm and the local legally applicable requirements.

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), ISO 14155: 2020, and applicable local regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), Independent Competent Ethics Committees (IEC) except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study maintain current Human Subjects Protection and ICH GCP Training certifications.

The protocol, informed consent form(s), recruitment materials (if applicable), and all participant materials will be submitted to the IRB/IEC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 800-898)
- ICH E6; 62 Federal Register 25691 (1997)

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site name:	
Principal investigator's name:	

Date (DD/MMM/YYYY) Signature

VERSION HISTORY

Version	Date	Effective Date	Changes
1.0	28 January 2020	n/a	Initial version. Part of IDE submission
1.1	13 May 2020	Each site can implement as soon it is approved by the required central and local authorities.	Administrative changes like correction of typos, font types and alignments. Patient word replaced in the document to subject. Local US Sponsor added. Facility of Coordinating Investigator in Europe is updated. Section 1.4 Investigational Site(s) added. Section 1.7 DSMB section is updated, Medical Monitor function and responsibility added. Section 2.1 updated to facilitate study registration in local required databases if needed. Section 2.6: "If an investigational site is suspended or prematurely terminated" paragraph added 3.6 section updated to better reflect the device distribution and software accessories activation in the study arms. Section 5.2 Secondary endpoint is updated with Fio_2 level assessment in both study arms. Section 5.2 VFD section is updated to clarify the 28D follow-up and definition of NIV is added. Clarification added how to calculate VFD and when study ventilation will end. Section 5.2 Dropout definition is updated and expected number of % is added.

Version	Date	Effective Date	Changes
			Section 5.2 updated with workload collection. Section 7.2 INC 5 is updated, subjects included in mechanical ventilation studies are excluded. Section 7.6.1 and 7.7 are added. Section 8.1 is added to clarify point of enrollment. Section E Tracheostomy section updated to reflect that these are only recommendations. Section 8.4 updated to be aligned with the VFD section. Section 9 is updated with ISO reference, MEDDEV reference, definition of UADE is added per 21CFR 812.3. Section 9.1.3 Recording and reporting AEs is updated. Section 9.1.1 Recording and reporting DD section added. 9.2 section update with Adverse Event Reporting requirements overview and timeline. 9.2.1 Emergency contact added. 10. Statistic section updated: O'Brien-Fleming-Type method is added instead of Wang-Tsiatis. Sample sizes and operational characteristics for the trial using O'Brien Fleming boundaries for futility and efficacy is added. Müller and Schäfer method is replaced by Following Metha and Pocock (Metha, 2011). Added to use the ITT population as the primary analysis population and the mITT for additional analyses.

Version	Date	Effective Date	Changes
			Table Values for optimal, acceptable and sub-optimal ranges is updated. Section 11.2.1 is updated to reflect that Memory Box will be used in both study arms to record data and it is compatible with Hamilton Ventilation devices used in both study arms. Section 11.3 is updated with potential Site qualification visit conduct. Section 11.5, 11.6 and 11.7 are added. Section 11.8 updated to further describe the confidentiality process. Section 11.10 is updated to better describe the reporting and assessment of protocol deviations. Section 12 is added. Section 15 is updated to indicate the applicable law.
2.0	02 October 2020	Each site can implement as soon it is approved by the required central and local authorities.	Administrative changes like correction of typos, font types and alignments. ClinicalTrials.gov Identifier: NCT04400643has been added throughout the document. European Coordinating investigator (Marco Maggiorini MD, Pr. deleted and added as an author) ISO reference data is updated to 2020. Abbreviation section is updated/corrected with ADE, AE, ASADE, CFR, CRF, CRRT, DD, EC , eCRF, HMV, IDH, IMDRF, MDCG, MDR, MEDDEV, SADE, UADE, USADE, VCLS and VigOps.

Version	Date	Effective Date	Changes
			Major changes are listed below: Summary of Subject evaluation test schedule is update to better reflect the order and timing of assessments. Furthermore the followings were added: Intubation status, Number of recruitment movers within the last observation period , Concomitant rescue therapies, Assessment of re-intubation status, Extubation failure, Acute kidney injury, Critical illness polyneuro –myopathy status, critical illness encephalopathy status, tracheostomy status, resusicated cardiac arrest status, other, Other imminently life-threatening experience, Barotrauma status Section 1.4 Blinded word added Section 2.6 following is added: If the Sponsor agrees to DSMB/ Medical Monitor recommendation to terminate the Study based on site recorded AE(s)/SAE(S) Section 3.1: clarification added since INTELLiVENT-ASV is a ventilation mode and the devices are supplier with it, but the clinician will set it as active or non-active . Section 5.2 Secondary safety outcomes updated with the followings: In addition to better characterize the risk profile of the study population the following non-mechanical ventilation related adverse events will be recorded on study day 7 and 28. • Sever Acute kidney injury (AKI) in need for CRRT/IHD • Sever critical illness neuro-myopathy signs of treaplegia

Version	Date	Effective Date	Changes
			affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for limb movement, but not against gravity and score 3 for movement against gravity but not resistance. • Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points. • Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ failure affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation. • Extubation failure that is related to weaning process by itself or associated conditions based on the interpretation of the investigator. • Need for tracheostomy that is related to a difficult weaning process or associated conditions

Version	Date	Effective Date	Changes
			based on the interpretation of the investigator. Section 7.3 : exclusion criteria updated with the followings: EXC #11 updated to have it better formulized: Decision to withhold or withdraw life support. This does not exclude those patients committed to full support except cardiopulmonary resuscitation. EXC # 18, 19 and 20 are added Section 7.5 : clarifications added on co-enrolment guidelines and DSMB role with co-enrolment decision. Section 7.6 Study Withdrawal updated to reflect that the 80% of the ventilation time within the allocated randomized ventilation mode needs to be recorded. Section 8.1: clarifications added on screening and baseline assessments. Followings added: Clarification added how to handle shortage of ventilators, limited resource. Section 8.1.2 Clarification added regarding point of enrolment: ICF signed dated & patient randomized. Section 8.2, 8.3, 8.4 and 8.5 updated to reflect the changes of the assessment schedule. Section 8.3.1 updated with the followings as well: If the subject's medical condition requires medical intervention (bronchoscopy, trancescopy, radiology or OR interventions…etc.) and the subject is

Version	Date	Effective Date	Changes
			allocated to the INTELLiVENT-ASV arm, the allocated randomized ventilation mode may be switched off for the required time period. This needs to be documented in the subject's medical chart. If the ventilation mode is modified by the site personnel by oversight or lack of training (deviating from the allocated randomization arm) and the subject's medical condition did not require it, the ventilation mode should be set back to allocated randomization arm. A protocol deviation and the event will be recorded in the eCRF accordingly. Section 9: Adverse Event reporting requirements is updated to align with the DSMB Chart based on DSMB members recommendations. Definitions added which AE/SAEs to be recorded by the site. List of AE is created that required to be recorded, please see Annex D. Definition of Study Specific outcome added. Adverse Event Review chart is added. Table of AE reporting requirements is restructured to be more simplified. Section 11.5 is updated to reflect that the site PI is responsible to determine that the study is no longer in the subject's best interest. Section 11.6.4: alignment in medical reporting requirements in US References is update with 2 new publications:

Version	Date	Effective Date	Changes
			1) Arnal JM, Saoli M, Garnero A. Airway and transpulmonary driving pressures and mechanical powers selected by INTELLiVENT-ASV in passive, mechanically ventilated ICU patients. Heart Lung. 2019 Nov 14:S0147-9563(19) 30533-3. 2) De Bie AJR, Serpa Neto A, van Meenen DM, Bouwman AR, Roos AN, Lameijer JR, Korsten EHM, Schultz MJ, Bindels AJGH. Fully automated postoperative ventilation in cardiac surgery patients: a randomised clinical trial. Br J Anaesth. 2020 Jul 29; S0007-0912(20)30497-9. doi: 10.1016/j.bja.2020.06.037. Online ahead of print. Annex A Clinical manifestations and medical occurrences, unintended diseases or injuries or clinical signs that are attributed to the concurrent illness / clinical condition of critically ill subjects in an ICU include[1]: is updated with the followings: • Congestive Heart failure right and left LV • Atrial flutter/fibrillation • Acute myocardial infraction • Abdominal hypertension/compartment Syndrome • Stroke • Intra cerebral bleeding Hemodynamic effects: PEEP is added

[1] Manufacturer´s State-of-the-Art Documentation, on file

Version	Date	Effective Date	Changes
			Annex D : addition of expected adverse event to be recorded by the investigators

Abbreviations

%MinVol	Minute ventilation expressed in percentage of IBW
ΔP	Driving Pressure
ADE	Adverse Device Effect
AE	Adverse Event
AKI	Acute kidney injury
APRV	Airway Pressure Release Ventilation
APV	Adaptive Pressure Ventilation
ARDS	Acute Respiratory Distress Syndrome
ASADE	Anticipated Serious Adverse Device Effect
ASV	Adaptive Support Ventilation
ATS	American Thoracic Society
CA	Competent Authority
CFR	Code of Federal Regulations
CRF	Case Report Form
CRRT	Continuous Renal Remplacement Therapy
CO	Carbon Monoxide
CO2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CMV	Continuous mandatory ventilation
CPAP	Continuous Positive Airway Pressure
DD	Device Deficiency

DSMB	Data Safety Monitoring Board
DuoPAP	Duo Positive Airway Pressure
EC	Ethics Committee
ECCO2R	Extracorporeal Carbon Dioxide Removal
ECMO	Extracorporeal Membrane Oxygenation
eCRF	electronic Case Report Form
FDA	US Food and Drug Administration
FiO2	Fraction of Inspiratory Oxygen
fSpont	Spontaneous Breathing Rate
H2O	Water
HFO	High Frequency Oscillatory Ventilation
HMV	Hamilton Medical Vigilance
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IHD	Intermittent haemodialysis
IMDRF	International Medical Device Regulation Forum
IoR	Investigator of Record
IRB	Institutional Review Board
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MEDDEV	Medical Device Vigilance
MV	Minute Volume
NIV	Non-Invasive Ventilation

O2	Oxygen
OHRP	Office for Human Research Protections
PaO2	Partial Pressure of Oxygen
PASV	Maximum inspiratory pressure limit setting
PCV	Pressure Control Ventilation
PEEP	Positive End-Expiratory Pressure
PetCO2	End-tidal partial pressure of carbon dioxide
Pmax	Maximum Pressure
P_{PLAT}	Plateau Pressure
RCexp	Expiratory time constant
RR	Respiratory Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SIMV	Synchronized Intermittent Mandatory Ventilation
SOFA	Sequential Organ Failure Assessment
SpO2	Oxygen Saturation Measured by Pulse Oximetry
TRC	Tube resistance compensation
T Tube	Method to perform a weaning trial that consist of disconnecting the subject from the ventilator
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VCLS	Voisin Consulting Life Sciences

VFD	Ventilator Free Day(s)
VigOps	Vigilance Operations
VT	Tidal Volume

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Clinical Investigation Synopsis

Sponsor:	Hamilton Medical AG, Via Crusch 8, CH 7402 Bonaduz, Switzerland
US Sponsor:	Hamilton Medical Inc., 4655 Aircenter Circle 4655 Reno NV 89502 USA
Study Title:	Prospective, multicenter, randomized, controlled study comparing efficacy and safety of INTELLiVENT-ASV versus Non-automated Ventilation in adult ICU subjects.
Short Title / Study ID:	EASiVENT
Protocol Version and Date:	Protocol Version 2.0 dated 02 October 2020
Trial registration:	ClinicalTrials.gov Identifier: NCT04400643
Study category and Rationale	IDE Study / PMCF in EFTA Results will serve as the primary basis for the determination of reasonable assurance of safety and efficacy of INTELLiVENT-ASV of a pre-market approval application (PMA) and the FDA's overall benefit-risk determination.
Clinical Phase:	Pivotal

Background and Rationale:	INTELLiVENT-ASV is a software accessory that automatically adjusts ventilation and oxygenation variables to keep the subject within clinician-set target ranges, from intubation until extubation. The INTELLiVENT-ASV is a closed-loop ventilation mode and is intended as an accessory for currently marketed Hamilton Medical ventilators. INTELLiVENT-ASV includes the following features: 1. Ventilation controller (% MinVol) 2. Oxygenation controller (FiO_2 & PEEP) 3. Quick Wean With INTELLiVENT-ASV, the clinician sets subject targets for $PetCO_2$ and SpO_2 and selects the subject's initial respiratory condition (normal lung, Acute Respiratory Distress Syndrome (ARDS), chronic hypercapnia or brain injury). The system automates the controls for CO_2 elimination (%MinVol) and oxygenation (PEEP and FiO_2) based on these targets and on the monitoring input from the subject ($PetCO_2$ and SpO_2). INTELLiVENT-ASV continuously monitors subject conditions and safely adjusts parameters to keep the subject within the predefined target ranges, with minimal clinician interaction, from intubation until extubation.
Primary Objective(s):	**Efficacy**: To assess the efficacy of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrollment. **Safety**: To assess the safety of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrollment.

Primary endpoints	**Efficacy** The primary efficacy endpoint will be to assess the ability to keep ventilation and oxygenation variables in optimal target ranges. This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range **during the 7 days after enrollment**: 1) Tidal volume (VT) 2) Maximum pressure (Pmax) 3) Oxygen saturation measured by pulse oximetry (SpO_2) 4) End-tidal partial pressure of carbon dioxide ($PetCO_2$) 5) Respiratory rate (RR) for spontaneous breathing subjects 6) Pmax-PEEP for passive ARDS subjects The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia. **Safety:** The primary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range during the 7 days after enrollment.

Secondary endpoints	Secondary endpoints will be measured continuously **up to 28 days** after enrollment. The secondary endpoints will assess ventilation safety and efficacy by measuring physiological variables, clinical outcomes, and associated interventions continuously up to 28 days after enrolment. **Efficacy** <u>Physiologic parameters</u>**:** 1) Respiratory mechanics (Compliance, resistance, expiratory time constant) will be assessed automatically breath-by-breath 2) Oxygenation (PaO_2/FiO_2, FiO_2, PEEP) 3) Ventilation (VT, RR, mechanical power will be assessed automatically breath-by-breath, ΔP, P_{PLAT}, will be assessed twice a day). 4) FiO_2 levels to be assessed in both study arms <u>Outcomes</u>**:** 1) Duration of invasive mechanical ventilation: time between intubation and last extubation or death. When a subject is re-intubated within 48 hours after extubation, the period between extubation and re-intubation is considered as invasive ventilation days. 2) Duration of non-invasive mechanical ventilation: noninvasive ventilation (NIV) refers to Continuous Positive Airway Pressure (CPAP) or pressure support NIV delivered before intubation or after extubation. High flow therapy is not considered in this calculation. 3) Total duration of mechanical ventilation: sum of duration of invasive and noninvasive mechanical ventilation. 4) Time from intubation to first successful Spontaneous Breathing Trial (SBT) 5) Passive ventilation duration: passive ventilation is defined when the percentage of subject's triggered breath is lower than 25% of total respiratory rate. 6) Weaning duration: time between the first sedation cessation to the last extubation or the last disconnection from the ventilator for tracheostomized subjects. Subjects reintubated within 48h after extubation will be kept in the study. Subject that are re-intubated beyond 48h will be considered as weaned from the ventilation.

	7) Ventilator free days (VFD) up to day 28: VFD to day 28 are defined as: the number of days from the time of initiating unassisted breathing to day 28 after start of ventilation, assuming survival for at least 48 hours and no re-intubation within 48 hours after initiating unassisted breathing and continued unassisted breathing to day 28. NIV will be considered as assisted breathing. CPAP will not be considered as assisted breathing. Ventilator free days will be calculated separately for invasive ventilation support and any other ventilation support (invasive and noninvasive). If a subject returns to assisted breathing (re-intubated within 48 hours) and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a subject was receiving assisted invasive breathing on day 27 or dies prior to day 28, VFDs will be -1. For subjects transferred to another hospital or other health care facility, study data collection will be stopped but subject will be contacted via a phone call on day 28 post enrollment to assess VFD endpoint if possible: • ICU and hospital length of stay (discharge). • ICU mortality (if the subjects is hospitalized in another hospital than the investigational site) • Non-intensive ventilation (NIV) duration • 28 days mortality • Ventilation duration for study period (if reintubated beyond 48h) • Tracheostomy

	Associated interventions: 1) Duration and doses of sedative infusion 2) Duration and doses of analgesic infusion 3) Duration and doses of vasopressors 4) Duration and doses of myorelaxant 5) Number of recruitment maneuvers 6) Time spent in prone position 7) Time spent with nitric oxide Workload: 1) Number of manual adjustment will be collected in both ventilation arms until considered as weaned from the ventilation. **Safety** The secondary safety endpoint will be determined by evaluating the number of Serious Adverse Events (all SAEs included) within 28 days of the enrollment and the rescue therapy requirement (APRV, high frequency ventilation, $ECCO_2R$ and ECMO). In addition to better characterise the risk profile of the study population the following non-mechanical ventilation related adverse events will be recorded on study day 7 and 28. • Severe Acute kidney injury (AKI) in need for Complete Renal Replacement Theray (CRRT)/intermittent haemodialysis (IHD) • Severe critical illness neuro-myopathy signs of tetraplegia affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for limb movement, but not against gravity and score 3 for movement against gravity but not resistance. • Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points. • Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ failure

	affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation.
	• Extubation failure that is related to weaning process by itself or associated conditions based on the interpretation of the investigator. • Need for tracheostomy that is related to a difficult weaning process or associated conditions based on the interpretation of the investigator.
Tertiary endpoints	Tertiary endpoints will be measured continuously during ventilation period **from day 8 up to day 28** after enrollment. **<u>Efficacy</u>** Efficacy of the investigational device by assessing the ability to keep ventilation and oxygenation variables in optimal target ranges. This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range during day 8 through day 28: 1) Tidal volume (VT) 2) Maximum pressure (Pmax) 3) Oxygen saturation measured by pulse oximetry (SpO_2) 4) End-tidal partial pressure of carbon dioxide ($PetCO_2$) 5) Respiratory rate (RR) for spontaneous breathing subjects 6) Pmax-PEEP for passive ARDS subjects The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia. Tertiary endpoints will be measured continuously during ventilation period **from day 8 up to day 28** after enrollment. **<u>Safety:</u>** The tertiary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range **from day 8 up to day 28 after enrollment**.

Study design:	Prospective, Multicenter, Randomized (1:1), Controlled Study. This study is single-blind because only the subject will be unaware of the ventilation modality administered. The reference treatment used for comparison is a combination of controlled modes for passive subjects (volume control or pressure control) and assisted/spontaneous modes for active subjects (synchronized intermittent mechanical ventilation or pressure support)
Study Population:	Eligible subjects are adult ICU subjects requiring invasive mechanical ventilation, 21 years and older and fulfilling the inclusion and exclusion criteria.
Inclusion / Exclusion criteria:	**Inclusion Criteria** Adults must fulfill all of the following inclusion criteria to be eligible for enrollment into this study: 1. Age ≥ 21 years old 2. Weight > 40 kilograms 3. Under invasive ventilation for less than 24 hours 4. Expected to be mechanically ventilated for at least 24 hours after enrollment 5. Agrees to not participate in other interventional research studies involving mechanical ventilation for the duration of study participation, unless approved by the DSMB 6. Signature of the informed consent by the subject or his/her next-of-kin according to country or state regulation

	Exclusion Criteria Adults who meet any of the following criteria are not eligible for enrollment into this study: 1. Fulfilling weaning criteria according to the weaning procedure of the ICU 2. Need for "rescue therapy" (ECMO, ECCO2R, HFO)) 3. Brain death status 4. Respiratory drive disorder (Cheyne-Stokes breathing) 5. Arterial hypoxia due to a non-pulmonary condition (right-to-left shunting due to congenital disease, hepato-pulmonary syndrome,) 6. Broncho-pleural fistula 7. Chronic or acute dyshemoglobinemia: acute CO poisoning, meth-hemoglobin, sickle cell disease. 8. Chronic respiratory failure requiring long term invasive ventilation; 9. Moribund subject: death expected within 24 hours 10. Positive pregnancy test at screening for childbearing age women 11. Decision to withhold or withdraw life support. This does not exclude those patients committed to full support except cardiopulmonary resuscitation. 12. Subject under guardianship 13. Subject deprived of liberties 14. Subject included in another interventional research study involving mechanical ventilation under consent. 15. Any other condition, that in the opinion of the IoR/designee, would preclude informed consent (by the spouse/next of kin), make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives 16. Low quality index on the SpO2 measurement using finger and ear sensor for > 3 hours 17. Subjects already enrolled in the present study in a previous episode of acute respiratory failure 18. High $PaCO_2$ – $ETCO_2$ gap (> 2.6 kPa or 19.5 mmHg) for > 3 hours 19. Patient tracheostomized at the time of inclusion 20. Patient ventilated with helium

Measurements and procedures:	Efficacy and Safety are measured by assessing the ability to keep ventilation and oxygenation variables in optimal target ranges: 1) Tidal volume (VT) 2) Maximum pressure (Pmax) 3) Oxygen saturation measured by pulse oximetry (SpO_2) 4) End-tidal partial pressure of carbon dioxide ($PetCO_2$) 5) Respiratory rate (RR) for spontaneous breathing subjects 6) Pmax-PEEP for passive ARDS subjects The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia. • Physiologic parameters • Outcomes • Associated interventions • Number of Serious Adverse Events
Study Product / Intervention:	INTELLiVENT-ASV, utilizing a Hamilton-Medical ventilator.
Control Intervention (if applicable):	Non automated Ventilation (administered according to the ICU protocols), utilizing Hamilton Medical ventilator.
Number of Participants with Rationale:	Minimum of 254 and a maximum of 508 subjects. An adaptive sample size reassessment is foreseen at the second interim analysis. The method used is the 'promising zone' approach. Following Mehta and Pocock (Mehta, 2011), sample sizes will only be increased in case the interim results are promising, in which case the overall type-I error is not inflated by use of the conventional Wald statistic.

Participant Duration:	Each enrolled subject will be followed for a maximum of 28 days. The Study Completion should be completed at the time when a subject completes the study in the Case Report Form (CRF). A subject will be considered to have completed the study for the following reasons: • Subject completes the follow-up visits the protocol as planned until Day 28. • Subject dies. • Subject or legally authorized representative requests to be withdrawn from the study. • Investigator requests that the subject is withdrawn from the study to protect the welfare of the subject. This is a decision based on site's Principal Investigator's judgement. Dropout could occur when subjects are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU or withdrawal of informed consent. A maximum dropout rate of 5% of these cases is expected.
Study Duration:	Accrual is expected to be completed in approximately 24 months.
Study Schedule:	Month Year of First-Participant-In (planned): Q4 2020 Month Year of Last-Participant-Out (planned): Q4 2022
Sponsor:	Hamilton Medical AG, Via Crusch 8, CH 7402 Bonaduz, Switzerland
US Sponsor :	Hamilton Medical Inc., 4655 Aircenter Circle 4655 Reno NV 89502 USA
US Principal Investigator:	**Omitted**
Study Centre(s):	Approximately twenty (20) sites with ICU capability in United States and European countries
Statistical Considerations:	*EASiVENT* hypothesizes that INTELLiVENT-ASV will outperform "Non automated Ventilation" on the Hamilton Medical Ventilators, in terms of efficacy and safety.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki 2013, the ICH-GCP or ISO 14155: 2020 (as far as applicable) as well as all national legal and regulatory requirements.

Data oversight	A Data Safety Monitoring Committee (DSMB) will be established to independently evaluate subject health status, device performance, and identify any safety concerns regarding subjects' well-being. Contact details of the committee will be available in the investigational site file.

Table 1: Summary of subject evaluation tests: schedule of assessments for both Study Arms.

The following clinical and research tests will be conducted with the following sequence during the study to assess eligibility, efficacy and safety

Study Period	**Screening**	**Baseline**	**Intervention Period**											**End of Study**	**Study Exit**
Time	**Day 0**	**Day 0**	**Day 0**	**Day 0**	**Day 1**	**Day 1**	**Day 2-3**	**Day 4**	**Day 4**	**Day 5-6**	**Day 7**	**Day 7**	**Day 8-27**	**Day XX**	**Day 28**
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-10	Visit 11	Visit 12	Visit 13-16	Visit 17	Visit 18	Visit 19-59	Visit 60	Visit 61
Inclusion/exclusion criteria	X														
Pregnancy Test	X														
Informed Consent	X														
Randomization	X														
Demographic Data		X													
Intubation/reintubation status	X	X			X	X	X	X	X	X	X	X	X	X	X
Acute Pulmonary Condition	X				X	X	X	X	X	X	X	X	X	X	X**
Medical history & comorbidity factors		X													
Current INTELLIVENT-ASV settings			X	X	X	X	X	X	X	X	X	X	X	X	
INTELLIVENT-ASV randomisation violation status			X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	
Ventilatory parameters manual assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	
24h Recording of ventilation parameters *(Memory Box)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood gas analysis (If available visit ± 2h)	X	X#	X	X	X	X	X	X	X	X	X	X	X	X	
ICU severity Scores (SAPS II, APACHE II)					X										
SOFA score					X			X			X			X	
Concomitant sedation, analgesia and myorelaxants use		X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant vasopressors and inotropics use		X		X	X	X	X	X	X	X	X	X	X	X	

Study Period	**Screening**	**Baseline**	**Intervention Period**											**End of Study**	**Study Exit**
Time	**Day 0**	**Day 0**	**Day 0**	**Day 0**	**Day 1**	**Day 1**	**Day 2-3**	**Day 4**	**Day 4**	**Day 5-6**	**Day 7**	**Day 7**	**Day 8-27**	**Day XX**	**Day 28**
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-10	Visit 11	Visit 12	Visit 13-16	Visit 17	Visit 18	Visit 19-59	Visit 60	Visit 61
Number of recruitment maneuvers within the last observation period				X	X	X	X	X	X	X	X	X	X	X	
Concomitant rescue therapies (proning, Nitric oxyde, ...)		X		X	X	X	X	X	X	X	X	X	X	X	
Weaning information NIV, CPAP, High Flow.)				X	X	X	X	X	X	X	X	X	X	X	
Screening of readiness to extubate criteria (SBT)						X	X	X	X	X	X	X	X	X	
Assessment of re-intubation status							X	X	X	X	X	X	X	X	
Extubation failure (yes/no)							X	X	X	X	X	X	X	X	X
Acute Kidney Injury (AKI) status and need vor RRT (yes/no)	X	X						X		Xf	X		Xf	X	X
Criticall illess polyneuro- myopathy status (yes/no)	X	X						X		Xf	X		Xf	X	X
Critcial illess encepahlopathy status (yes/no)	X	X						X		Xf	X		Xf	X	X
Tracheostomy status (yes/no)											X		Xf	X	X
Resuscitted cardiac arrest status (yes/no)								X			X			X	
Other imminently life-threatening experience								X			X			X	
Barotrauma status (yes/no)								X			X			X	
Rescue therapy requirement (APRV, HFO, ECCO2R and ECMO).														X	
Patient status incl. Withhold of weaning and/or withdrawald of MV														X	X**
Ventilation duration for study period *(if reintubated beyond 48h)*														X	
ICU and hospital length of stay														X	X**
ICU/Hospital death														X	X**

Study Period	Screening	Baseline	Intervention Period											End of Study	Study Exit
Time	**Day 0**	**Day 0**	**Day 0**	**Day 0**	**Day 1**	**Day 1**	**Day 2-3**	**Day 4**	**Day 4**	**Day 5-6**	**Day 7**	**Day 7**	**Day 8-27**	**Day XX**	**Day 28**
Time specifications		T0	T0+1h	T0+6h (only if T0 before 12 a.m.)		morning visit time + at leat 6h			mornig visit time + at least 6h			morning visit time + at least 6h			
Visit #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7-10	Visit 11	Visit 12	Visit 13-16	Visit 17	Visit 18	Visit 19-59	Visit 60	Visit 61
Adverse Event collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X**

Legend

* 24H recording of ventilation parameters include: Ventilator settings, Alarm settings and Breath-by-breath monitoring of: Tidal volume (VT), total Respiratory rate (RR), spontaneous RR, inspiratory time, expiratory time, Maximum pressure (Pmax), Oxygen saturation measured by pulse oximetry (SpO_2), End-tidal partial pressure of carbon dioxide ($PetCO_2$), PEEP, inspiratory flow, expiratory flow, static compliance for passive subjects, inspiratory resistance for passive subjects, expiratory time constant.

ƒ to be assesst only in the morning visit.

if ventilator settings have changed since visit 1

1 STUDY ADMINISTRATION AND STRUCTURE

1.1 Sponsor

Hamilton Medical AG, Via Crusch 8, CH 7402 Bonaduz, Switzerland

US Sponsor: Hamilton Medical Inc., 4655 Aircenter Circle Reno NV 89502 USA

1.2 Principal Investigator(s)

Omitted

1.3 Investigational Site(s)

Investigational sites will be located both in Europe and in US.

The list of sites with contact details of the study team and principal investigators is maintained in the Trial Master File and provided to the investigators.

1.4 Statistician ("Biostatistician")

An independent blinded statistician from IDDI will be in charge of optimizing the study design and performing the statistical analysis.

1.5 Monitoring institution

VCLS will be in charge of monitoring activities at sites.

Voisin Consulting Life Sciences
64, avenue Pierre Grenier
92100 Boulogne Billancourt
France

1.6 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be settled by the sponsor and will be composed experts in mechanical ventilation independent from the study coordinators and investigators.

The responsibility of the DSMB is to evaluate safety data during the course of the trial and to advise Hamilton Medical about the continuing safety of the Study.

Listings of recorded Adverse Events/Serious Adverse Events and Device Deficiencies will be provided by VCLS VigOps to the Independent Medical Monitor to evaluate safety of the study device. All events,

including any device related events will be reviewed on a case by case base by the Independent Blinded Medical Monitor. A safety concern raised by the Independent Medical Monitor triggers a DSMB meeting. Trial data will be reviewed on a periodic basis as defined in the DSMB Charter.

Based on the available safety data, the DSMB may recommend that Hamilton Medical modify or terminate the trial. DSMB composition, duties, procedures, deliberation rules are detailed and documented in the DSMB Charter.

2 ETHICAL AND REGULATORY ASPECTS

2.1 Study registration

Study is registered at ClinicalTrials.gov, ClinicalTrials.gov Identifier: NCT04400643.

Study registration in any other databases that might be required per local requirements/regulations will be done by the sponsor or designee.

2.2 Institutional Review Board (IRB) / Independent Competent Ethics Committee (EC)

It is the responsibility of the investigator and of Hamilton Medical to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator Site File. Copies of IRB/EC approvals should be forwarded to Hamilton Medical.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent hazards to the subjects. In that event, the investigator must notify the IRB/EC and Hamilton Medical in writing immediately after the implementation.

2.3 Competent Authorities (CA)

Competent authorities will be notified prospectively by Hamilton Medical as need be. The sponsor, Hamilton Medical, will be ultimately responsible for ensuring that competent authorities' approvals are approved in target countries.

2.4 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (2013), the guidelines of Good Clinical Practice (GCP) issued by ICH and in accordance to local regulation law.

2.5 Declaration of interest

Site investigator will complete financial disclosure form (Form 3455), 21 CFR Part 54.

2.6 Suspension or Premature Termination of the Clinical Investigation

This study may be discontinued at any time by Hamilton Medical, the US FDA, OHRP, other government or regulatory authorities, or site IRB(s)/EC(s).

The Sponsor may decide to stop the study early or close a site in the following situations:

- If the Sponsor received information about the Investigational device which is liable to change the benefit/risk balance;
- In the event of inadequate recruitment within the predetermined time on the site,
- If the Investigator received information about the investigational device or resources that may jeopardize the conduct the study;
- If the Sponsor considers that the results of the Clinical Study are not scientifically convincing;
- If the objective of the study is no longer relevant or of interest;
- If the Investigator fails to meet of his/her fundamental obligations through the terms of this agreement, and particularly a breach of the Clinical Study Protocol, a breach of the current laws and regulations or a breach of Good Clinical practices requirements;
- If the total number of subjects recruited is achieved earlier than planned;
- If it is a regulatory decision;
- If the Sponsor agrees with DSMB/ Medical Monitor's recommendation to terminate the Study based on site recorded AE(s)/SAE(S).

In all situations, the Sponsor will inform the Investigator of its decision in writing.

If an investigational site is suspended or prematurely terminated:

- The investigator shall then promptly inform enrolled subjects
- The investigator agreement will be terminated
- The investigator will inform the institution
- Sponsor will inform the Regulatory Authority(ies) (where required by applicable regulatory requirements)

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and IEC/IRB, if applicable.

3 BACKGROUND AND RATIONALE

Mechanical ventilation is the first line supportive treatment of acute respiratory failure in ICU subjects and ensures the replacement of gas exchange during respiratory failure in ICU subjects (2). Ventilation support should be adapted to cellular metabolism in order to provide necessary oxygen (oxygenation) and to eliminate carbon dioxide (ventilation).

In conventional ventilation modes, clinicians adjust and modify the oxygenation and ventilation parameters manually. Subjects in an ICU evolve continually, and parameters may not be optimal with manual adjustments (3). These manual adjustments represent a substantial workload for clinicians during subject care (4), as conventional ventilation modes compel them to adjust all parameters and modify adjustments when the physiological status of the subject changes.

Some ventilation modalities adjust ventilation automatically according to physiological parameters measured on the subject (5, 6). They have been proven beneficial with regards to ventilation optimization as adapted in real time to subject clinical condition, decreased care workload and ventilation duration (7, 8, and 9). Unnecessary high FiO_2 leading to hyperoxemia is detrimental. The ability to adjust FiO_2 to subject needs is likely beneficial for subjects and reduce costs. Currently, no automated oxygenation control is available on marketed ventilators for adult subjects in the US.

Adaptive Support Ventilation mode (ASV) has been used for 21 years in Europe and INTELLiVENT-ASV software accessory received CE marking in 2010 in Europe. It is a software accessory that fully automates Hamilton Medical's ASV mode, automatically adjusting both oxygenation and ventilation settings (10). The oxygenation parameters, FiO_2 and PEEP, are adjusted according to oxygen saturation measured by pulse oximetry (SpO_2). Ventilation is adjusted according to end-tidal partial pressure of carbon dioxide measurement ($PetCO_2$) in passive subjects (without spontaneous ventilation) and according to respiratory rate (RR) and $PetCO_2$ in active subjects (with spontaneous ventilation). The system can stabilize the subject in these optimal zones with maximum safety.

When target MV is determined, tidal volume (VT) and RR are determined according to the principle of the least respiratory work and force of breathing (11, 12). Clinicians choose target ranges for SpO_2 and $PetCO_2$ in addition to the limits for FiO_2, PEEP, and inspiratory pressure.

INTELLiVENT-ASV safety and efficacy have been demonstrated in post-cardiac surgery (13) and in ICU subjects over periods of time up to 48 hours (10, 14). A randomized, cross-over, pilot study comparing INTELLiVENT-ASV mode to ASV in fifty (50) passive ICU subjects in Europe demonstrated better efficacy of ventilation, by delivering less volumes and pressures without alteration of gas exchange (10). The automatically selected parameters remained within the defined safety limits. The present study will assess safety and efficacy of INTELLiVENT-ASV in ICU subjects up to 7 days after enrollment.

3.1 Investigational device(s) and comparator(s)

Non automated ventilation arm:

Non automated ventilation mode (administered according to the ICU protocols), utilizing Hamilton Medical ventilator.

For those ventilators used for treating the subjects in the non-automated ventilation mode INTELLiVENT-ASV ventilation mode will not be selected.

It will be evaluated on a site by site cases if Hamilton Medical ventilators will be supplied by the Sponsor to be used for this study in the non-automated ventilation arm.

If there is a need to have the ventilators provided by the Sponsor upon completion of evaluation, Sponsor will supply the devices.

Automated ventilation arm:

INTELLiVENT-ASV ventilation mode, utilizing a Hamilton-Medical ventilator.

For those subjects in the automated arm the INTELLiVENT-ASV ventilation mode will be selected.

Sponsor will supply ventilation system, to be used for this study, if needed.

All subjects will be ventilated with a Hamilton ventilator equipped with SpO_2 and $PetCO_2$ sensors in order to assess the main endpoints.

INTELLiVENT-ASV is a software accessory that automatically adjusts ventilation and oxygenation parameters to keep the subject within clinician-set target ranges, from intubation until extubation.

It is a closed-loop ventilation mode and is intended as an accessory for currently marketed Hamilton Medical ventilators.

INTELLiVENT-ASV includes the following features:

1. Ventilation controller (% MinVol)
2. Oxygenation controller (FiO_2 & PEEP)
3. Quick Wean

The investigator brochure provides details on physiological inputs and sensor management.

Please refer to the Investigator Brochure for more details

3.2 Preclinical Evidence

Preclinical evidence is included in the Investigator Brochure.

3.3 Clinical Evidence to Date

Please refer to Annex B

3.4 Risks and Benefits Statement

Risks

Subjects suffering from critical illness and requiring invasive mechanical ventilation are exposed to numerous risks. First, critical illness in and of itself can cause numerous complications and mechanical ventilation may not always prevent a fatal outcome related to the underlying disease. Second, invasive mechanical ventilation is an invasive, potentially prolonged procedure that exposes the subject to specific risks of complications related to: Airway management (tracheal tube intubation), need of analgesia and sedation, infection, critical-illness neuromyopathy and thrombosis. Even in situations where mechanical ventilation can help improve gas exchange, inappropriate ventilator settings can lead to: ventilator-induced lung injury, lung barotrauma (pneumothorax) and iatrogenic alterations in O_2 and CO_2 arterial blood content. There is mounting evidence that not only low O_2 and high CO_2, but also low CO_2 and high O_2 can be deleterious to the critically ill subject. In short, the risks of invasive mechanical ventilation should be lower than the risks of the critical illness. Clinicians involved in the management of critically ill subjects continuously try to minimize these risks by periodical arterial blood gas sampling leading to regular iterative adjustments of the settings of the ventilator. In some instances, a continuous monitoring of $PetCO_2$ and SpO_2 is performed. Strategies aiming at limiting sedation and detecting as soon as possible the ability of the subject to be liberated from the ventilator are also systematically implemented, to minimize the time spent under invasive mechanical ventilation.

Both groups will be exposed to the risks inherent to invasive mechanical ventilation, such as ventilator malfunction and error in arterial blood gas measurements. Each ICU has specific strategies and policies to prevent and handle such problems.

Conceivably, risks specific to INTELLiVENT-ASV include erroneously setting respiratory condition or ideal body weight and sensor malfunction. To minimize the risk of erroneous setting, a specific training will be provided to all healthcare workers handling subjects included in the study (**refer to Annex C)**. Regarding sensor malfunction, INTELLiVENT-ASV per design handles such occurrence by interrupting the close-loop automatic adaptations, keeping the ongoing setting and alarming the ICU team to the condition. They will then have the choice either to correct the sensor failure (a typical example would be a dislodged SpO_2 sensor due to subject's movement) or to enter new settings manually as in the control group. Furthermore, the attending physician has at any time the possibility to switch to conventional ventilation if she/he deems it necessary.

Although the above-mentioned situations are theoretically possible, preliminary studies have shown that among different groups of subjects, there is a safer ventilation with INTELLiVENT-ASV compared to conventional ventilation in volume (13).

Subjects are monitored as any ICU subject, with particular attention to ventilation parameters. The attending physician in the ICU always has the possibility to fall back to conventional ventilation for whatever reason.

The risk level is estimated to be moderate. The INTELLiVENT-ASV system was the subject of a risk analysis, and preliminary studies have not reported any adverse events related to INTELLIVENT-ASV during more than 200 hours of cumulative ventilation with INTELLiVENT-ASV (10, 13).

Benefits

The common health field benefit is to make available to this subject population, a ventilator that continuously adapts the delivered ventilation and oxygenation in real time to the needs of mechanically ventilated ICU subjects. These automations are a real progress in relation to the current procedures and above all may increase the safety of mechanically ventilated subjects.

The individual risk faced is therefore limited, and alarm settings can alert the physician in order to immediately correct as needed any ventilation or oxygenation anomaly. The potential overall benefit is high for ICU subjects. The benefit / risk balance does justify the study conduct as there is no additional risk anticipated for subjects – there may be the possibility to detect additional clinical benefits as outlined before.

4 STUDY OBJECTIVES

4.1 Overall objectives of the study

The study is designed to assess safety and efficacy of INTELLiVENT-ASV, a software accessory integrated in Hamilton ventilators that is designed to fully and automatically adjust both oxygenation and ventilation settings.

Efficacy and safety are primarily assessed to keep ventilation and oxygenation variables in optimal target ranges according to pertinent guidelines for Invasive Mechanical Ventilation.

4.2 Primary Objectives

Efficacy: To assess the efficacy of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrollment.

Safety: To assess the safety of INTELLiVENT-ASV in adult ICU subjects up to 7 days after enrollment.

4.3 Secondary Objectives

The secondary objective is the assessment of ventilation safety and effectiveness by measuring physiologic parameters, clinical outcomes associated interventions and typical clinical complications up to day 28 after enrollment.

4.4 Tertiary Objectives

Efficacy: To assess the efficacy of INTELLiVENT-ASV in adult ICU subjects from day 8 up to day 28 after enrollment.

Safety: To assess the safety of INTELLiVENT-ASV in adult ICU subjects from day 8 up to day 28 after enrollment.

5 STUDY ENDPOINTS

5.1 Primary endpoints

Primary endpoints will be measured continuously during ventilation period up to 7 days after enrollment.

Efficacy

Efficacy of the investigational device by assessing the ability to keep ventilation and oxygenation variables in optimal target ranges.

This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia.

Safety:

The primary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range during the first seven (7) days of enrollment.

For the invasive mechanical ventilation ranges, please refer to section 10.4.5 Analysis of Primary Endpoints.

5.2 Secondary endpoints

Secondary endpoints will be recorded continuously until the end of intervention period (up to 28 days after enrollment).

Efficacy

Physiologic parameters:

1. Respiratory mechanics (Compliance, resistance, expiratory time constant) will be assessed automatically breath-by-breath
2. Oxygenation (PaO_2/FiO_2, FiO_2, PEEP)
3. Ventilation (VT, RR, mechanical power will be assessed automatically breath-by-breath, ΔP, P_{PLAT}, will be assessed twice a day).

4. FiO_2 levels to be assessed in both study arms

Outcomes:

1. Duration of invasive mechanical ventilation: time between intubation and last extubation or death. When a subject is re-intubated within 48 hours after extubation, the period between extubation and re-intubation is considered as invasive ventilation days.
2. Duration of non-invasive mechanical ventilation: noninvasive ventilation refers to CPAP or pressure support NIV delivered before intubation or after extubation. High flow therapy is not considered in this calculation.
3. Total duration of mechanical ventilation: sum of duration of invasive and noninvasive mechanical ventilation.
4. Time from intubation to first successful SBT
5. Passive ventilation duration: passive ventilation is defined when the percentage of subject's triggered breath is lower than 25% of total respiratory rate.
6. Weaning duration: time between the first sedation cessation to the last extubation or the last disconnection from the ventilator for tracheostomized subjects. Subjects reintubated within 48h after extubation will be kept in the study. Subject re-intubated beyond 48h will be considered as weaned from the ventilation.
7. VFD to day 28 are defined as: the number of days from the time of initiating unassisted breathing to day 28 after start of ventilation, assuming survival for at least 48 hours and no re-intubation within 48 hours after initiating unassisted breathing and continued unassisted breathing to day 28.

   NIV will be considered as assisted breathing. CPAP will not be considered as assisted breathing. Ventilator free days will be calculated separately for invasive ventilation support and any other ventilation support (invasive and noninvasive).

   If a subject returns to assisted breathing (re-intubated within 48 hours) and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28.

   A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation.

   If a subject was receiving assisted invasive breathing on day 27 or dies prior to day 28, VFDs will be - 1.

   For subjects transferred to another hospital or other health care facility, study data collection will be stopped but subject will be contacted via a phone call on day 28 post enrollment to assess VFD endpoint if possible:
   - ICU and hospital length of stay (discharge).

- ICU mortality (if the subjects is hospitalized in another hospital than the investigational site)
- Non-intensive ventilation (NIV) duration
- 28 days mortality
- Ventilation duration for study period (if reintubated beyond 48h)

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent. A maximum dropout rate of 5% of these cases is expected.

Associated interventions:

1. Duration and doses of sedative infusion
2. Duration and doses of analgesic infusion
3. Duration and doses of vasopressors
4. Duration and doses of myorelaxant
5. Number of recruitment maneuvers
6. Time spent in prone position
7. Time spent with nitric oxide

Workload:

1. Number of manual adjustment will be collected in both ventilation arms until considered as weaned from the ventilation.

Safety:

The secondary safety endpoint will be determined by evaluating the number of Serious Adverse Events (all SAEs included) within 28 days of the enrollment and the rescue therapy requirement (APRV, high frequency ventilation, ECCO2R and ECMO).

In addition to better characterise the risk profile of the study population the following non-mechanical ventilation related adverse events will be recorded on study day 7 and 28.

- Severe Acute kidney injury (AKI) in need for CRRT/IHD
- Severe critical illness neuro-myopathy signs of tetraplegia affecting arms shoulder and neck with potential implication of respiratory muscle. Weakness is documented using the following score points: score 0 for no visible muscle contraction, score 1 for visible muscle contraction with no or trace movement, score 2 for limb movement, but not against gravity and score 3 for movement against gravity but not resistance.
- Severe critical illness encephalopathy leading to prolongation of mechanical ventilation. The most frequent causes being a metabolic or electrolyte disorder, systemic inflammation and other causes. Hypoxia, Stroke, intracranial bleeding, epilepsy and delirium. Encephalopathy is assessed using the GCS score and need to be reported is < 8 points.
- Withhold of weaning and/or withdrawal of mechanical ventilation because of treatment limitation related to patient wish or treatment futility due to irreparable single or multi-organ

failure affect mechanical ventilation strategy, weaning from mechanical ventilation up to withdrawal of mechanical ventilation.

- Extubation failure that is related to weaning process by itself or associated conditions based on the interpretation of the investigator.
- Need for tracheostomy that is related to a difficult weaning process or associated conditions based on the interpretation of the investigator.

5.3 Tertiary endpoints

Tertiary endpoints will be measured continuously during ventilation period **from day 8 up to day 28** after enrollment.

Efficacy

Efficacy of the investigational device by assessing the ability to keep ventilation and oxygenation variables in optimal target ranges.

This endpoint will be determined by the percentage of time spent with six (6) variables in the optimal range:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO_2)
4) End-tidal partial pressure of carbon dioxide ($PetCO_2$)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

The optimal and sub-optimal ranges are defined by pertinent guidelines for different clinical conditions including normal lungs, brain injury, ARDS, and chronic hypercapnia.

Tertiary endpoints will be measured continuously during ventilation period **from day 8 up to day 28** after enrollment.

Safety:

The tertiary safety endpoint will be determined by percentage of time spent with at least one variable in the sub-optimal range **from day 8 up to day 28 after enrollment**.

6 STUDY DESIGN

6.1 General

EASiVENT is a Pivotal, two-arm, controlled, single-blind, multicenter, randomized trial of INTELLiVENT-ASV versus non automated Ventilation in adult ICU subjects.

6.2 Methods of minimizing bias

6.2.1 Randomization

The subjects will be randomized to either INTELLiVENT-ASV or Non automated Ventilation using in a 1:1 ratio by a computerized central randomization system.

The two study arms will be stratified by subject condition at inclusion (normal lungs, ARDS, chronic hypercapnia, or brain injury) and by site to ensure balanced assignment for interventions at each site. The randomization scheme will be generated and maintained by the randomization module part of the electronic case report form (eCRF).

6.2.2 Blinding

Study subjects will be blinded to the random intervention assignment. Therefore, this study is considered single blind since study staff will know each subject's intervention assignment.

6.3 Justification for the design of the clinical investigation

The reference treatment used for comparison is a combination of controlled modes for passive subjects (volume control or pressure control) and assisted/spontaneous modes for active subjects (synchronized intermittent mechanical ventilation or pressure support).

Sample size has been adjusted with an adaptive design to be able to fulfill the targeted endpoints (see section 10.2)

7 STUDY POPULATION

7.1 Selection of the Study Population

Eligible patients are adult ICU subjects, 21 years and older, requiring invasive mechanical ventilation and fulfilling the inclusion and exclusion criteria.

ICU patients will be selected from sites in Europe and in US. Recruitment will be competitive.

7.2 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for enrollment into this study:

1. Age ≥ 21 years old
2. Weight > 40 kilograms
3. Under invasive ventilation for less than 24 hours
4. Expected to be mechanically ventilated for at least 24 hours after enrollment
5. Agrees to not participate in other interventional research studies involving mechanical ventilation for the duration of study participation, unless approved by the DSMB
6. Signature of the informed consent by the subject or his/her next-of-kin according to country or state regulation

7.3 Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for enrollment into this study:

1. Fulfilling weaning criteria according to the weaning procedure of the ICU
2. Need for “rescue therapy” (ECMO, ECCO2R, HFO))
3. Brain death status
4. Respiratory drive disorder (Cheyne-Stokes breathing)
5. Arterial hypoxia due to a non-pulmonary condition (right-to-left shunting due to congenital disease, hepato-pulmonary syndrome,)
6. Broncho-pleural fistula
7. Chronic or acute dyshemoglobinemia: acute CO poisoning, meth-hemoglobin, sickle cell disease.
8. Chronic respiratory failure requiring long term invasive ventilation;
9. Moribund subject: death expected within 24 hours
10. Positive pregnancy test at screening for childbearing age women
11. Decision to withhold or withdraw life support. This does not exclude those patients committed to full support except cardiopulmonary resuscitation.
12. Subject under guardianship
13. Subject deprived of liberties
14. Subject included in another interventional research study involving mechanical ventilation under consent.

15. Any other condition, that in the opinion of the IoR/designee, would preclude informed consent (by the spouse/next of kin), make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.
16. Low quality index on the SpO2 measurement using finger and ear sensor for > 3 hours
17. Subjects already enrolled in the present study in a previous episode of acute respiratory failure
18. High PaCO2 – ETCO2 gap (> 2.6 kPa or 19.5 mmHg) for > 3 hours
19. Patient tracheostomized at the time of inclusion
20. Patient ventilated with helium

7.4 Vulnerable Population

Pregnant Women

Any female with childbearing potential that tests positive for pregnancy at screening is not eligible to participate in this study.

Subject under guardianship/ Subject deprived of liberties

Any subject who is under guardianship or deprived of liberties is not eligible to participate in this study.

Children

This study will not enroll persons under the age of 21 years.

7.5 Co-enrollment Guidelines

As indicated in Sections 7.2 and 7.3 above, subjects are not permitted to take part in other research studies involving mechanical ventilation for the duration of study participation while taking part in *EASiVENT*, unless approved by the DSMB. Should any participant (or friend, family member, etc.) report concurrent participant in another research study after enrollment into *EASiVENT* not previously approved by the DSMB, the IoR/designee must consult the DSMB regarding ongoing participation and potential safety considerations associated with co-enrollment.

7.6 Study Withdrawal

Participants (or spouse/next of kin or legally authorized representative) may voluntarily withdraw from this study for any reason at any time, regardless of the participant retention strategies utilized. Additionally, the IoR may also withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with primary investigator and Hamilton Medical. Participants may be withdrawn from the study if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs/ECs terminate the study prior to its planned end. Every reasonable effort will be made to complete a final evaluation of participants who withdrawal/terminate early from the study, and study

staff will record the reason(s) for all withdrawals in the participants' study records. In addition, subject withdrawal will be documented in the eCRF on the End of Study forms.

If subjects are transferred after seven (7) days of start of ventilation, primary endpoints will be assessed and study ventilation protocol ended. However, the ventilation duration and mortality will be captured on Day 28 after enrollment via a phone call as described in VFD section.

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent. We expect a maximum of 5% of these cases.

Note a maximum of 5% of subjects are anticipated for which not 80% of mechanical ventilation time, within the allocated randomized ventilation mode, could be recorded due to documented technical reason.

Please refer to: Section 10.5 "Missing Data"

7.6.1 Lost-to-follow-up

A subject is to be considered lost to follow-up once the investigator and/or research staff has made three documented attempts to contact the subject in case of Day 28 data collection and the subject is not reachable. The third attempt should be made by certified mail to the subject.

In case the required data of Day 28 is available in the national/site database there is no need to send out a certified mail to the subject.

7.7 Medical care after study exit

After the subjects exit the study (Day 28 data collection completed), the subject will be followed as per routine standard of care. No long-term follow-up is planned per the protocol.

7.8 Informed Consent Process

Written informed consent will be obtained from each study participant, spouse/next of kin or a legally authorized representative. As the protocol is dealing with ICU subjects, it is anticipated that most of subjects are in a life-threatening situation and it is not feasible to obtain their informed consent as a result of their medical condition. In that case, a legally authorized representative or a family member of the subject will be asked to provide consent and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible.

Each study site will have their site specific study informed consent form(s) for local use that describes the purpose of the study, randomization and the importance of participation in both study interventions to the success of the study, the procedures to be followed, the risks and benefits of participation, the distinct between research and clinical care, and the right to withdraw from the study at any time, in accordance with all applicable regulations. If applicable, the study site is also responsible for translating the template form into the local language, and verifying the accuracy of the translation by performing an independent back-translation.

All USA sites will cover the elements required per Office for Human Research Protections (OHRP) CFR §46.116 - Informed Consent Checklist - Basic and Additional Elements in their local consent forms.

Each participant (or spouse/next of kin or a legally authorized representative) will document his/her provision of informed consent by signing his/her informed consent form.

Each signed and dated consent must be maintained by the clinical investigator and a copy of the informed consent must be provided to the subject.

8 STUDY PROCEDURES

8.1 Screening and Point of Enrollment process

8.1.1 Screening

Patient's eligibility will be determined by the investigator or designee based upon the followings:

1. The availability of Hamilton's ventilators designated for the study.
    a. If subject's participation will be waived due to lack of device availability it will be documented on the study Pre-Screened subjects log.
    b. If the number of eligible patient is greater than the number of the available ventilators that are designated for the study, the chronological order to ICU admission (date & time) must be respected.

2. Site personnel workload assessment:
   If subject's participation will be waived due to resource limitation of the study team, the chronological order to ICU admission (date & time) must be respected and the reason will be documented on the study Pre-Screened subjects log.

3. Pregnancy test (for female subjects of childbearing potential). Test must be completed per institutional standard of care at the time of screening. Results must be negative.

4. Investigators or designee will assess if the potential patient is expected to be on invasive mechanical ventilation for more than 24 hours based upon review of their medical history and disease progress for inclusion in the trial.

   If the patient appears to meet the eligibility criteria, and is expected to be ventilated for more than 24 hours:

    a. Then the investigator will discuss the study with the patient or next-of-kind or a legally authorized representative and provide information relating to the potential risks and benefits, and required follow-up procedures per the informed consent process, and
    b. The investigator will check that the patient did not express his/her right to object to participate in the study in any identifiable manner, including obtaining clear oral information from any available relative(s) on the patient's will.

   After the patient or next-of-kind or a legally authorized representative has voluntarily signed and dated the Informed Consent Form (ICF), the patient will be considered as a study candidate.
   If a the patient and or the next-of –kind or a legally authorized representative does not sign the ICF or the patient expressed his/her right to object to participate in the study in any identifiable manner, then no further study specific screening procedures can occur.

   The consenting process has to be documented in the subject source data.

8.1.2 Point of Enrollment and Randomization:

Subjects or next-of-kind or a legally authorized representative who sign and date the ICF and meet all of the study eligibility criteria will be eligible for inclusion into the EASiVENT Study.

Two different scenarios might occur:

1. The patient is already under invasive ventilation (intubated) for less than 24 hours, the next-of-kind or a legally authorized representative will sign and date the ICF.
2. The patient is able to sign and date the ICF before intubation.

The subject will only be considered enrolled when the **ICF signed and dated** and the subject will be **randomly assigned (1:1)** to automate ventilation with INTELLiVENT-ASV or to the non-automated ventilation.

Randomization will be stratified according to the clinical condition at inclusion (normal lungs, ARDS, chronic hypercapnia, brain injury). According to randomization allocation, the subject's attending physician will adjust the ventilator settings and recording will start.

Recording of ventilation data will start as randomization is completed and allocated randomization mode is selected.

Enrolled subjects will be documented on the Screening and Enrolment Log.

The investigator will maintain a log of all subjects screened and enrolled in the clinical study, assigning an identification code linked to their names, alternative subject identification or contact information. Patients who do not qualify for enrollment will be documented as ineligible on the Screening and Enrollment log.

Adverse Event collection will be started after point of enrollment.

8.2 Baseline Assessment (Day 0)

Collection of baseline information will take place only after the subject or next-of-kind or a legally authorized representative has given voluntary, documented informed consent and will include the following:

- Intubation status
- Demographic data : gender, age, height (measured at entry time), actual weight;
- Vital signs: blood pressure, pulse rate and temperature
- Subject comorbidity & medical history (including pulmonary and cardiovascular medical history) and acute pulmonary condition;
- Ventilator parameters manual assessment
- 24h Recording of ventilation parameters (Memory Box)

- Concomitant rescue therapies (proning, Nitric oxyde, ...)
- Acute Kidney Injury (AKI) status and need for RRT (yes/no)
- Critical illness encephalopathy status (yes/no)
- Blood gas analysis
- Criticall illess polyneuro- myopathy status (yes/no)
- Adverse Event collection

All concomitant medications including sedation, analgesic, myorelaxants, concomitant vasopressors, inotropics use and the drugs used to treat chronic diseases.

Ventilation start date/time as well as ventilation parameters will be recorded in the eCRF.

In addition, main ventilation variables used for analysis will be recorded breath by breath:

- Tidal volume (VT);
- Respiratory rate (RR);
- Maximum pressure (Pmax);
- Oxygen saturation measured by pulse oximetry (SpO_2);
- End-tidal partial pressure of carbon dioxide ($PetCO_2$).

Plateau pressure and total PEEP will be measured by inspiratory and expiratory occlusions respectively at regular intervals and recorded in the electronic Case Report Form (eCRF) twice a day during the passive ventilation period.

8.3 Intervention Period (Day 1-Day 27):

8.3.1 General management in both groups

From inclusion up to day of extubation (and not reintubated within 48h after extubation), ventilation settings will be adjusted by the attending physician or respiratory therapist. Subject condition, sedation, analgesic and vasopressor use, and one blood gas analysis will be collected twice a day if blood gas analysis is done routinely by the ICU department, otherwise ventilation parameters will only be collected.

Subjects will be monitored by the attending physicians and all ventilation variables will be continuously recorded from inclusion to extubation or death. Except for ventilation, all other procedures and care (sedation, hemodynamics, glycemic control, etc.) will be conducted according to the protocols of the site by the subject's attending physicians.

Data listed below will be captured in the eCRF:

- Intubation/reintubation status
- INTELLIVENT-ASV randomization violation status
- Vitals signs: Blood pressure, pulse rate and temperature;
- Acute pulmonary condition;
- 24h Recording of ventilation parameters (Memory Box)

- Ventilation settings
- All concomitant medications including sedation;
- SOFA will be repeated at day 3 and 7, in order to follow the evolution of organ failure.
- Memory Box recording
- Blood gas analysis
- Severity scores based on the most abnormal values in oxygenation and laboratory results in the last 24h period (day 0):
    - Simplified Acute Physiology Score (SAPS II)
    - Acute Physiology and Chronic Health Evaluation (APACHE II)
    - SOFA score
- Concomitant sedation, analgesia and myorelaxants use
- Concomitant vasopressors and inotropics use
- Number of recruitment movers within the last observation period
- Concomitant rescue therapies (proning, Nitric oxyde, ...)
- Weaning information associated interventions (Patient Passive/Active but still on MV, NIV, CPAP, High Flow.)
- Advers Event collection

Recorded data has to be 24 hours at minimum and 80% of the invasive ventilation duration within the allocated randomized ventilation mode have to be recorded in the in Memory Box.

If the subject's medical condition requires medical intervention (bronchoscopy, trancescopy, radiology or OR interventions…etc) and the subject is allocated to the INTELLiVENT-ASV arm, the allocated randomized ventilation mode may be switched off for the required time period. This needs to be documented in the subject's medical chart.

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU, or withdrawal of informed consent. We expect a maximum of 5% of these cases. Note a maximum of 5% of subjects are anticipated for which not 80% of mechanical ventilation time could be recorded within the allocated randomized ventilation mode due to documented technical reason. The recorded data will be used (with 'percent spent' calculated per the recorded time) for the primary analysis of the co-primary endpoints. As a sensitivity analysis, these values will be treated as missing data.

If the ventilation mode is modified by the site personnel by oversight or lack of training (deviating from the allocated randomization arm) and the subject's medical condition did not require it, the ventilation mode should be set back to allocated randomization arm. A protocol deviation and the event will be recorded in the eCRF accordingly.

If the site's principal investigator determines that the study is no longer in the subject's best interest (including the randomized ventilation mode) the subject's ventilation and study data collection ends. The site needs to complete an AE and the End of Study eCRF.

A. Gas exchanges targets:

SpO_2 will be kept in the ranges:

- 94 - 98% for normal lung, mild and moderate ARDS, and brain injured subjects
- 90-96% for moderate ARDS
- 88 - 95% for severe ARDS
- 90 - 94% for COPD without chronic hypoxemia or hypercapnia
- 88 - 92% for chronic hypercapnic subjects or subjects on long term oxygen

$PaCO_2$ will be kept in the range:

- 35 - 40 mm Hg for brain injury
- 35 - 50 mm Hg for normal lung, mild and moderate ARDS, COPD subjects without chronic hypercapnia
- ≥ 50 mm Hg in severe ARDS, severe COPD, and subjects with chronic hypercapnia if pH > 7.25

B. Passive subjects:

i. Ventilator settings:

Tidal volume will be kept in the range:

- 6-10 mL/Kg IBW for normal lung subjects, brain injury, and COPD subjects
- 4-8 mL/Kg IBW for ARDS

ii. Lung protection monitoring:

Plateau pressure will be measured at least twice a day and kept below 30 cmH_2O. Driving pressure will be measured at least four times a day and kept below 15 cmH_2O in all subjects.

In ARDS subjects, Plateau pressure between 30 and 35 cmH_2O will be accepted if driving pressure remains below 15 cmH_2O.

If plateau pressure exceeds 35 cmH_2O or driving pressure exceeds 15 cmH_2O, tidal volume will be decreased by 1 mL/Kg IBW keeping it above 4 mL/Kg or inspiratory pressure will be decreased by 2 cmH_2O.

iii. Additional and rescue procedures:

Continuous myorelaxant infusion, repeated recruitment maneuvers, nitric oxide, and prone position will be considered as additional procedures at the clinician's discretion.

If PaO_2 ≥ 55 mmHg or SpO_2 ≥ 88% with FIO_2 of 1.0 cannot be maintained, clinicians may employ rescue procedures. APRV, high frequency ventilation, ECCO2R and ECMO will be considered as a rescue therapies. The subjects will continue to be followed and included in the analysis on an intention-to-treat basis. Failure of the protocol and subsequent need for rescue therapy will constitute a secondary outcome. Control group subjects will not be allowed to cross-over to the INTELLiVENT-ASV group.

C. Spontaneous breathing subjects:

i. Ventilator settings:

Ventilation support will be adjusted to keep tidal volume in the range:

- 6-10 mL/Kg IBW for normal lung subjects, brain injury, and COPD subjects

- 4-8 mL/Kg IBW for ARDS

Ventilation support will be adjusted to keep respiratory rate ≤ 35 Breaths/min.

Inspiratory trigger settings will be set between 1 and 5 L/min or 0.5 and 2 cmH_2O or activate Intellisync+.

Expiratory trigger setting will be set between 10 and 80% of the maximal inspiratory flow or activate Intellisync+.

Pressure rise time will be set between 0 and 400 ms.

Automated tube compensation if appropriate.

D. Weaning:

The INTELLiVENT-ASV or control arm ventilator protocols will be continued until subjects are able to breathe unassisted for 48 hours, death, ICU discharge, study withdrawal, if the site's principal investigator determines that the study is no longer in the subject's best interest or day 28, whichever comes first.

i. Screening of readiness to wean criteria

A screening of readiness to wean criteria will be performed twice a day between 6h00 and 18h00 for all subjects mechanically ventilated for more than 24h.

ii. Extubation

After a successful weaning trial, extubation criteria will be assessed:

- Coma Glasgow Score > 8
- Ability to cough
- Ability to swallow
- Absence of severe upper airway obstruction
- Successful cuff leak test

If all these criteria are fulfilled, subject will be extubated within 12 hours after the successful weaning trial.

iii. Ventilation management after extubation

High flow nasal treatment, CPAP, and NIV can be used after extubation.

iv. Definition of unsuccessful extubation

If reintubation occurs within 48-hours of extubation, this event will be noted as a reintubation.

v. Completion of ventilator procedures.

Subjects will be considered to have completed the study ventilator procedures if any of the following conditions occur:

1. Death
2. ICU discharge
3. Subject or proxy withdraws consent

4. Principal investigator of site determines that the trial is no longer in the subject's best interest
5. Completed a period of 48 hours of unassisted breathing.

If a subject requires positive pressure ventilation after a period of unassisted breathing, these will be at the discretion of the team caring for the subject.

E. Tracheostomy

The following recommendations to be consider for Tracheostomy.

Tracheostomy will only be performed on strict indications and preferably not earlier than 10 days after intubation.

Indications for tracheostomy will be:

- Failure to intubate
- Expected duration of mechanical ventilation > 14 days
- Glasgow Coma Score < 7 and/or inadequate swallow or cough reflex with sputum retention
- Severe ICU-acquired weakness
- Prolonged or unsuccessful weaning
- Repeated respiratory failure after extubation

Readiness to wean criteria will be the same as intubated subjects. The weaning schedule for unassisted ventilation with a tracheostomy will follow the local protocol of the participating centers.

F. Sedation

Sedation will be prescribed with a sedation target using RASS or RAMSAY scale re-assessed at least once a day. Sedation will be monitored at least 2 times a day.

A daily cessation of sedation will be performed if there is no contraindication.

The subject's study follow up ends after 28 days after enrollment, even if subject remains on mechanical ventilation. During this 28 days period, for subjects reintubated within 48h after extubation, VFD will not be counted and ventilator protocols will be continued. Subject re-intubated beyond 48h will be considered as weaned for ventilator and ventilator procedures will not be continued.

8.3.2 Ventilation protocol in non-automated ventilation group

In order to standardize the non-automated ventilation process, Investigators will aim to keep the control arm (conventional non-automated ventilator) as close to the standard of care of the participating sites as possible.

General approach: The overall goals for the control arm ventilation protocol will be similar to those in the INTELLiVENT-ASV group including all recommendation available regarding gas exchanges targets, ventilator settings, protective ventilation targets, and weaning management (16, 32).

A. Passive subjects:

i. Ventilation mode

Any controlled mode will be possible such as volume control (CMV), pressure control (P-CMV), dual mode (APVcmv and APVsimv), DuoPAP, SIMV, and P-SIMV. APRV will not be accepted. Tube resistance compensation (TRC) can be added.

ii. Ventilator settings

Respiratory rate will be adjusted according to $PaCO_2$ with a maximum of 35 Breaths/min.

Table 2: Management of pH and PaCO2:

pH < 7.15 Increase Respiratory rate up to 35 b/min and keep PaCO2 > 25 mm Hg	pH= 7.15 – 7.29 Increase Respiratory rate up to 35 b/min and keep PaCO2 > 25 mm Hg	pH= 7.29 – 7.45 Maintain VT around 6 mL/kg IBW in ARDS subjects and between 6 – 8 mL/Kg IBW for other subjects and maintain respiratory rate below 35 b/min.	pH > 7.45 Decrease respiratory rate but not below 6 /min
Consider $NaHCO_3$ If needed increase VT by 1 ml/Kg IBW or increase P_{INSP} by 2 cmH2O with a maximum VT at 8 mL/Kg IBW for ARDS subjects and 10 mL/Kg IBW for other subjects. P_{PLAT} can be higher than 35 cmH2O in case of extreme acidosis.	Consider $NaHCO_3$ If needed increase VT by 1 ml/Kg IBW or increase P_{INSP} by 2 cmH2O with a maximum VT at 8 mL/Kg IBW for ARDS subjects and 10 mL/Kg IBW for other subjects. Keep P_{PLAT} ≤ 35 cmH2O.		If needed decrease VT by 1 ml/Kg IBW or decrease P_{INSP} by 2 cmH2O with a minimum VT at 4 mL/Kg IBW for ARDS subjects and 5 mL/Kg IBW for other subjects.

PEEP will be set using PEEP/FiO_2 table, PEEP trial or transpulmonary pressure (based on the local hospital protocol).
PEEP will be kept in the range:
- 5-10 cmH_2O for normal lung subjects and COPD
- 5-25 cmH_2O for ARDS subjects
- 5-15 cmH_2O for obese subjects
FiO_2 will be adjusted to the lowest to achieve SpO_2 target.

B. Spontaneous breathing subjects:

i. Ventilation mode:

Any assisted and spontaneous mode will be possible such as pressure support (SPONT), volume support (VS), SIMV, P-SIMV, and DuoPAP. APRV will not be accepted.

ii. Ventilator settings:

Ventilation support will be adjusted to keep tidal volume in the range:
- 6-10 mL/Kg IBW for normal lung subjects, brain injury, and COPD subjects
- 4-8 mL/Kg IBW for ARDS
Ventilation support will be adjusted to keep respiratory rate ≤ 35 Breaths/min.
PEEP will be kept in the range:
- 5-10 cmH_2O for normal lung subjects and COPD
- 5-15 cmH_2O for ARDS and obese subjects

C. Weaning

The INTELLiVENT-ASV or control arm ventilator protocols will be continued until subjects are able to breathe unassisted for 48 hours, death, ICU discharge, study withdrawal, the Principal investigator of the site determines that the study is no longer in the subject's best interest or day 28, whichever comes first.

i. Weaning trial

When the readiness to wean criteria will be fulfilled, a weaning trial will be performed on the same day for a duration of 30 min by any method with PEEP ≤ 5 cmH_2O and PS ≤ 7 cmH_2O: CPAP, tube compensation, minimal pressure support, T tube, or tracheostomy mask.

8.3.3 Ventilation protocol in INTELLiVENT-ASV ventilation group

Subject allocated to INTELLiVENT-ASV group will be ventilated with this mode from inclusion to the end of the study. Tube resistance compensation (TRC) can be added.

A. Passive subjects:

i. Ventilator settings:

Clinician will set the IBW, subject condition, $PetCO_2$ and SpO_2 targets, PEEP ranges, and alarms and activate the controllers. The minimal FiO_2 will be set at 0.21. An arterial blood gas will be performed 30-60 min later in order to adjust the PetCO2 target.

Table 3: Management of pH and $PaCO_2$:

pH < 7.15 Decrease $PetCO_2$ targets by 5 mm Hg and keep $PaCO_2$ > 25 mm Hg Consider $NaHCO_3$	pH= 7.15 – 7.29 Decrease $PetCO_2$ targets by 5 mm Hg and keep $PaCO_2$ > 25 mm Hg Consider $NaHCO_3$	pH= 7.29 – 7.45 No change	pH > 7.45 Increase $PetCO_2$ targets by 5 mm Hg

ii. Controller deactivation

PEEP and FiO_2 controller will be transiently deactivated if it is not possible to get a good SpO_2 signal with both finger and ear sensors. SpO_2 signal quality will then be re-assessed every 6h in order to restart oxygenation controller as soon as possible.

PEEP controller is by design deactivated when brain injury and chronic hypercapnia conditions are selected. PEEP will be set manually as in the non-automated ventilation group.

PEEP controller will not be deactivated in normal and ARDS conditions. Clinician can adjust PEEP ranges and use very narrow ranges if it is clinically needed.

Ventilation controller will be de-activated only if the clinical condition needs a %MV below 70% or above 200%.

Reasons and duration of controllers de-activation will be recorded in the eCRF.

B. Spontaneous breathing subjects:

i. Ventilator settings:

Clinician will set the IBW, subject condition, $PetCO_2$ and SpO_2 targets, PEEP ranges, and alarms and activate the controllers. The minimal FiO_2 will be set at 0.21. An arterial blood gas will be performed 30-60 min later in order to adjust the $PetCO_2$ target.

PEEP will be kept in the range:

- 5-10 cmH_2O for normal lung subjects and COPD
- 5-15 cmH_2O for ARDS and obese subjects

C. Weaning:

Weaning in the INTELLiVENT-ASV group will use quick wean function.

i. Quick wean activation

Quick wean will be activated when subject is stabilized with absence or minimum doses of sedation and vasopressor.
If subject has a coma Glasgow score above 8, quick wean function will be activated with SBT.
If subject has a coma Glasgow score below or equal to 8, quick wean function will be activated without SBT initially and SBT will be activated when the coma Glasgow score is above 8.

ii. Quick wean settings

Observation time will be set at 30 min before starting SBT.
Period between 2 SBT will be adjusted by the clinician according to the clinical needs.
Default settings to start SBT will be used:
PEEP ≤ 8 cmH2O
FiO_2 ≤ 40%
Tolerance time: 180 s
RR ≤ 35 b/min
Minimum VT ≥ 5 mL/kg IBW
Rapid Schallow Breathing index ≤ 105
PS between 5 and 12 cmH2O

iii. Weaning trial

Weaning trial will use the automatic SBT of the quick wean option with a PEEP of 5 cmH_2O, a %MV at 25%, and a duration of 30 min.
Criteria to abort SBT will be:

- PEEP > 8 cmH2O for the duration of tolerance time
- FiO_2 > 50% for the duration of tolerance time
- Tolerance time: 180 s
- RR > 35 b/min for the duration of tolerance time
- Minimum VT < 5 mL/kg IBW for the duration of tolerance time
- Rapid Schallow Breathing index > 105 for the duration of tolerance time
- PS > 12 cmH2O
- RR increase > 50%
- $PetCO_2$ increase > 8 mm Hg
- Apnea defined by a spontaneous RR below the target RR determined by ASV controller
- SpO_2 sensor failure

iv. Extubation

After a failed SBT, the clinician may decide to repeat it the same day or to stop SBT for some time, keeping the quick wean function active.

After a successful SBT, clinician will check the extubation criteria. If all criteria are fulfilled, extubation will be performed within 12 h.

8.3.4 Measurements

Breath-by-breath ventilation variable will be recorded during the full duration of study period.

On top of that, ΔP, Pplat, total PEEP, and blood gas results (if performed) will be measured twice a day and reported on the eCRF.

Information of acute pulmonary condition will be recorded in the eCRF.

Information about controllers de-activation and weaning process will be reported on a daily basis on the eCRF.

All concomitant medications will be recorded in the eCRF including sedation.

8.4 End of study (extubation + 48 hours):

The end of study visit should be completed at the time a subject completes the study ventilation protocol. It means that the subject is extubated and there is no need for re-intubation within 48 hours.

Subject reintubated within 48h after extubation will continue to be ventilated per the allocated randomized ventilation mode.

Subject re-intubated beyond 48h will be considered as weaned for the ventilation procedure. They remain in the study but only a phone call will be done on Day 28.

Following data point to be collected and recorded:

- Intubation/ re-intubation status
- Acute Pulmonary Condition
- Vital Signs
- Ventilator parameters manual assessment
- 24h Recording of ventilation parameters (Memory Box)
- Blood gas analysis (If available visit ± 2h)
- SOFA score
- Concomitant sedation, analgesia and myorelaxants use
- Concomitant vasopressors and inotropics use
- Number of recruitment maneuvers within the last observation period
- Concomitant rescue therapies (proning, Nitric oxyde, ...)
- Weaning information associated interventions (Patient Passive/Active but still on MV, NIV, CPAP, High Flow.)
- Screening of readiness to extubate criteria (SBT)
- Assessment of re-intubation status

- Extubation failure
- Acute Kidney Injury (AKI) status and need for RRT
- Critical illness polyneuro- myopathy status
- Critical illness encephalopathy status
- Tracheostomy status
- Resuscitated cardiac arrest status
- Other imminently life-threatening experience
- Barotrauma status
- Rescue therapy requirement (APRV, high frequency ventilation, $ECCO_2R$ and ECMO).
- Withhold of weaning and/or withdrawal of mechanical ventilation status
- Ventilation duration for study period (if reintubated beyond 48h)
- ICU and hospital length of stay
- ICU mortality (if subjects hospitalized somewhere else) or 28 Days mortality
- Adverse Event collection

8.5 Study Exit (Day 28):

Prior to completion of study close out, all subject data must be captured and monitored in the eCRF.

A subject will be considered to have completed the study for the following reasons:

- Subject completes follow-ups (Day 28) required per investigational plan.
- Subject dies.
- Subject or legally authorized representative requests to be withdrawn from the study.
- Investigator requests to be withdrawn from the study to protect the welfare of the subject. (In that case, it is at the site's principal investigator's discretion to determine that the study is no longer in the subject's best interest.)

In case of sponsor's decision to stop the study, the site will be notified by the sponsor in written of the intention to close the study. Study close out visits are then to be performed. During these visits, the monitors will ensure that the investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. The site will be informed that all requirements have been met with a study closure letter.

Following data point to be collected and recorded:

- Intubation status
- Acute Pulmonary condition
- Extubation failure - with SBT
- Acute Kidney Injury (AKI) status and need for RRT

- Critical illness polyneuro- myopathy status
- Critical illness encephalopathy status
- Tracheostomy status
- Ventilation duration for study period (if reintubated beyond 48h)
- ICU and hospital length of stay
- ICU mortality
- Adverse Event collection

8.6 Supply and Accountability

Ventilation system serial number utilized for each subject will be documented and placed in the subject's study file.

8.7 Ancillary Supplies

Additional equipment or consumables such as heated humidifier, ventilator circuit, flow sensor, SPO_2 sensor and CO_2 sensor cupula will be supplied by Hamilton Medical, if needed. The ancillary supplies have all market authorization in US and European country sites.

9 SAFETY

Please refer to:

Annex A
Identification of Risks and Adverse Events (AE´s) for the intended subject population, the clinical background and the device in question identified from clinical experience for INTELLiVENT-ASV

Annex D: List of Adverse Event
List of reportable Adverse Event

9.1 Recording and reporting of AEs

- **Recording:** Entry of an event into the clinical database by site staff as they "become aware" (Soladis System) or into the safety database by the safety team (VigOps). .
- **Reporting:** Sending a report to the National Competent Authority, EC/IRB. Sites are responsible for submitting reports to their IRB or EC in most countries.

The EASiVENT study includes a general ICU patient population in need of mechanical ventilation for at least 24 hours. This population includes critically ill patients spanning a variety of primary and secondary medical conditions that can cause AEs including severe disability and death irrespective of study participation. The expected mortality in EASiVENT Study patient population is around 30%.

Given the high acuity of diseases and morbidity related to ICU patient populations, not all AEs will be reported in the EASiVENT Study.

AE information will be collected throughout the study and reported to Hamilton Medical on the Adverse Event collected in the eCRF. The investigator is responsible for detecting, documenting and reporting AEs to Hamilton Medical through the eCRF or via a paper form if the eCRF is not available.

For AEs that require immediate reporting (see Table 4: Adverse Event Reporting Requirements), initial reporting may be done using the Events Form via email to VCLS VigOps (contact details will be provided in the investigational site file), or in the Serious Adverse Events form in the eCRF with as much information as is available. In case the investigator requires information from the Sponsor in an emergency situation, the contact details for emergency situations are given in the investigational site file.

Investigators in the US should submit Unanticipated Device Effects (UADEs) to their IRBs at the same time as notifying VCLS VigOps.

9.1.1 Study-Specific Clinical Outcomes

A list of anticipated AEs (AAEs) that are expected from underlying disease states are listed in Annex A of protocol– ***" Clinical manifestations and medical occurrences, unintended diseases or injuries or clinical signs that are attributed to the concurrent illness / clinical condition of critically ill subjects in an ICU include"****.*

All AEs that are listed under the above mentioned section of Annex A will be classified as *"study-specific clinical outcomes*", as these AE(s) are by their nature, incidence, severity, and outcome previously identified in the risk analysis report and the State-of-the-Art analysis.

Study-specific clinical outcomes of patients in need of mechanical ventilation will be recorded in eCRF as secondary outcomes and **will not be recorded** as AEs ***unless*** the investigator deems the AE to be possibly, probably or definitely (causal) related to the mechanical ventilation itself (or lead to permanent discontinuation of study interventions (except death events that are considered as study specific clinical outcomes)), in which case such events would be recorded as (AEs).

The following AE(s) will be considered study-specific clinical outcomes:

1. Death related to the underlying illness or associated conditions based on the interpretation of the investigator.
2. Significant hemodynamic instability, defined as (a) norepinephrine-equivalent vasopressor dose initiation or increase from any dose that is both double and at least 0.15 mcg/kg/min increased over ≤ 60 minutes to maintain blood pressure target OR (b) dobutamine-equivalent inotropic dose initiation or increase from any dose that is both double and at least 5 mcg/kg/min over ≤ 60 minutes to maintain cardiac output target in case of left or right ventricular dysfunction/failure) that is related to the underlying illness or associated conditions based on the interpretation of the investigator
3. Progression of respiratory failure as demonstrated by new post-enrollment use of respiratory rescue therapy (e.g. ECMO, $ECCO_2R$, inhaled vasodilators, prone positioning), that is related to progression of the underling illness or associated conditions based on the interpretation of the investigator.
4. Anoxic brain injury that is related to the underling illness or associated conditions based on the interpretation of the investigator
5. Extubation failure that is related to progression of the underling illness or associated conditions based on the interpretation of the investigator.
6. Need for tracheostomy that is related to progression of the underling illness or associated conditions based on the interpretation of the investigator.

9.1.2 Adverse Events (AEs)

ISO 14155 / MDR 2017/745 Definition (regulatory definition):

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, (including an abnormal laboratory finding,) in subjects, users or other persons, in the context of a clinica investigation, whether or not related to the investigational medical device. and whether anticipated or unanticipated.

NOTE 1 to entry: This definition includes events related to the investigational medical device or the comparator.
NOTE 2 to entry: This definition includes events related to the procedures involved.

NOTE 3 to entry: For users or other persons, this definition is restricted to events related to investigational medical devices.

Specificities to EASiVENT:

The following Adverse Events ***(AEs) will be recorded during*** the EASiVENT Study Days 0 through 28:

1. Serious Adverse Events (SAEs) other than those listed as study-specific outcomes
2. Non-serious AEs that are considered by the investigator to be possibly, probably, or definitely (causally) related to mechanical ventilation as a supportive measure for acute respiratory failure.
   For details please refer to EASiVENT Study list of Adverse Event**, Annex D**
3. AEs that lead to permanent discontinuation of INTELLiVENT-ASV-Management.

Investigators will be instructed to record their assessment of the potential relatedness of each Adverse Event (AE) to protocol procedures and mechanical ventilation. Potential relatedness of an event to mechanical ventilation will be determined by evaluating the temporal relationship and if the event is unanticipated or unexplained given the patient's clinical course, care, and previous medical conditions. The degree of certainty the investigator has regarding relatedness of the event to mechanical ventilation will be recorded as not related, possibly related, probably related, or definitely (causal) related. If patient's INTELLiVENT-ASV-Management is discontinued as a result of an AE, study site personnel will clearly record in the eCRF of the Study the circumstances and data leading to discontinuation of INTELLiVENT-ASV as ventilation mode.

By the nature of this patient population a myriad of ***non-serious Adverse Events (AEs)*** will occur during the Study. Due to the complexity of critical illness, it may be difficult for the investigators to classify whether an Adverse Event (AE) is related or not to the underlying condition or the sequelae of it or to mechanical ventilator support.

Therefore, investigators will be instructed that events such as:

a. transitory hypertension or
b. hypotension, tachy- or bradycardia,
c. arrhythmias (such as atrial fibrillation, heart block, ventricular tachycardia, or ventricular fibrillation),
d. transitory hypoxemia or
e. hypercapnia,
f. impaired cognitive function due to sedation/analgesia or delirium (see AE list attached),

Are not considered study population specific clinical outcomes and ***should be recorded*** as adverse events **only** if they are **serious** events ***or are considered to be related to mechanical ventilation or lead to discontinuation of INTELLiVENT-ASV mode***.

The blinded medical monitor and DSMB will evaluate investigator-reported SAEs and AEs and independently assess potential relatedness to study procedures and, where indicated, make recommendations for safety modifications to the protocol, temporary suspension, or even termination of the study.

9.1.3 Serious Adverse Event (SAE)

ISO 14155 / MDR 2017/745 Definition (regulatory definition):

An SAE is any adverse event that led to any of the following:

a) led to a death

b) led to a serious deterioration in health of the subject, users or other persons as defined by one or more ofthat resulted in any of the following:

- *a life-threatening illness or injury, or*
- *a permanent impairment of a body structure or a body function, including chronic diseases, or*
- *in-subject hHospitalization or prolongation of existing patient hospitalization, or*
- *in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,*
- *Chronic disease,*
- *led to foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment physical or mental impairment or birth defect.*

Specificities to EASiVENT:

SAE recording begins after the patient has signed informed consent and has received INTELLiVENT-ASV or standard of care mechanical ventilation (point of enrollment). If a patient experiences a SAE after signing informed consent, but prior to receiving the study intervention, the event will not be recorded unless the investigator feels the event may have been caused by a study procedure.

SAEs will be collected Day 0 through Day 28 of the study period or until extubation, whichever occurs first. Thereafter, SAEs are not required to be recorded unless the investigator feels the events were possibly, probably, or definitely (causal) related to study procedures.

An SAE is any Adverse Event (AE) that results in one of the following events and is not classified as a study-specific clinical outcome using the definitions enumerated above:

1. Death that is not related to the underlying illness or associated condition or death that is possibly, probably, or definitely (causal) related to study procedures
2. Resuscitated cardiac arrest that is not related to the underlying illness or associated condition, or that is possibly, probably, or definitely (causal) related to study procedures
3. Significant hemodynamic instability defined as (a) norepinephrine-equivalent vasopressor dose initiation or increase from any dose that is both double and at least 0.15 mcg/kg/min increased over > 60 minutes to maintain blood pressure target OR (b) dobutamin-equivalent inotropic dose initiation or increase from any dose that is both double and at least 5 mcg/kg/min over > 60 minutes to maintain cardiac output target in case of right ventricular dysfunction/failure, that is not related to the underlying illness or associated condition or that is possibly, probably, or definitely (causal) related to study procedures

4. Gross barotrauma (pneumothorax, pneumomediastinum, or subcutaneous emphysema) requiring chest tube or other surgical intervention, where the apparent barotrauma is not related to a procedural complication (e.g., a central venous catheter insertion causing pleural injury)
5. Significant hypercapnic acidemia ($PaCO_2$ > 60 mm Hg and pH < 7.20 with Vt > 8 ml/kg PBW and RR > 30 b/min) for at least two consecutive arterial blood gas measurments 60 min apart
6. Significant hypocapnic alkalemia ($PaCO_2$ < 30 mm Hg with pH > 7.50) for at least two consecutive arterial blood gas 60 min apart
7. Significant hypoxemia (oxygen saturation < 85% or PaO_2 < 55 mm Hg with FiO_2 1.0) sustained for at least 30 minutes for at least two consecutive arterial blood gas measurments 60 min apart
8. Progression of respiratory failure as demonstrated by new post-enrollment use of respiratory rescue therapy (e.g. ECMO and $ECCO_2R$), if it is considered as related (possibly, probably, definitely (causal)) to the ventilation mode and neither to the underlying illness nor associated conditions based on the interpretation of the investigator.
9. Hypoxic brain injury, which must be documented with a confirmatory neuroimaging and other clinical evaluations as per local routine practice as applicable , a documented significant hypoxemia event (defined above) during study participation, that is not related to the underlying illness or associated condition
10. Other imminently life-threatening event that is not related to the underlying illness or associated condition or that is possibly, probably, or definitely (causal) related to study procedures
11. Site investigator decides to change the allocated ventilation mode because if it is considered as related (possibly, probably, definitely (causal)) to the ventilation mode and neither to the underlying illness nor associated conditions based on the interpretation of the investigator.

9.2 Recording and reporting of Device Deficiencies (DDs)

DD information will be collected throughout the study and reported to Hamilton Medical. DDs should be recorded in on the Serious Adverse Event Form in the eCRF. In case the eCRF is not available the Event form needs to be completed manually and must be sent to VCLS VigOps team. Contact details are given in the investigational site file. The investigator is responsible for reporting all DDs to the Sponsor.

See the Serious Adverse Event eCRF for the information to be reported for each DD.
DDs that did not lead to an AE but could have led to a SAE:

a) If either suitable action had not been taken,
b) If intervention had not been made, or
c) If circumstances had been less fortunate,

Require immediate reporting (see Table 4: Adverse Event Reporting Requirements). Initial reporting may be done by eCRF, or using the Event Form via email to VCLS VigOps, with as much information as available. In case the AE/DD is related to an investigational Hamilton Medical device used during the study the VCLS VigOps team will ensure prompt review, and appropriate reporting.

9.2.1 Device deficiency (ISO 14155)

Inadequacy of an medical device related to its identity, quality, durability, reliability, usability, safety or performanc

9.2.2 Adverse Device Effect (ADE) *(ISO 14155)::*

Adverse event related to the use of an investigational medical device.

NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2: This also includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Note 3 to entry*:* this includes 'comparator' if the comparator is a medical device.

9.2.3 Serious Adverse Device Effect (SADE) *(ISO 14155):*

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.2.4 Anticipated SADE (ASADE)

ISO 14155 Definition (Regulatory definition)

Effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Specificities to EASiVENT:

The INTELLIVENT-ASV ventilation mode was launched in the year 2010. Since then 3576 INTELLiVENT-ASV software accessories have been sold worldwide.

Today, there has been no reported problems, events, serious adverse events or recalls due to the INTELLiVENT-ASV accessory software on HAMILTON ventilators. The vigilance database searches for Bfarm (the German database and the largest European database for medical device adverse event reporting) did not yield any events, reported problems, serious adverse events due to or related to INTELLiVENT-ASV.

9.2.5 Anticipated Serious Adverse Device Effect from risk management activities of the manufacturer:

Anticipated Serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report are the following, please refer to **Annex A**

9.2.6 Unanticipated Adverse Device Effect (UADE): (21 CFR 812.3)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2.7 Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155):

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

AEs, SAEs, ADEs, SADEs and USADEs are included in the "incident" definition for post-market vigilance.

NOTE 1 to entry: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

9.2.8 Serious Health Threat (ISO 14155)

A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

Note *1* to entry: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

9.2.9 Incident (MEDDEV 2.12-1)

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or user or of other persons or to a serious deterioration in their state of health.

Figure 1: Adverse Events Categorisation Chart

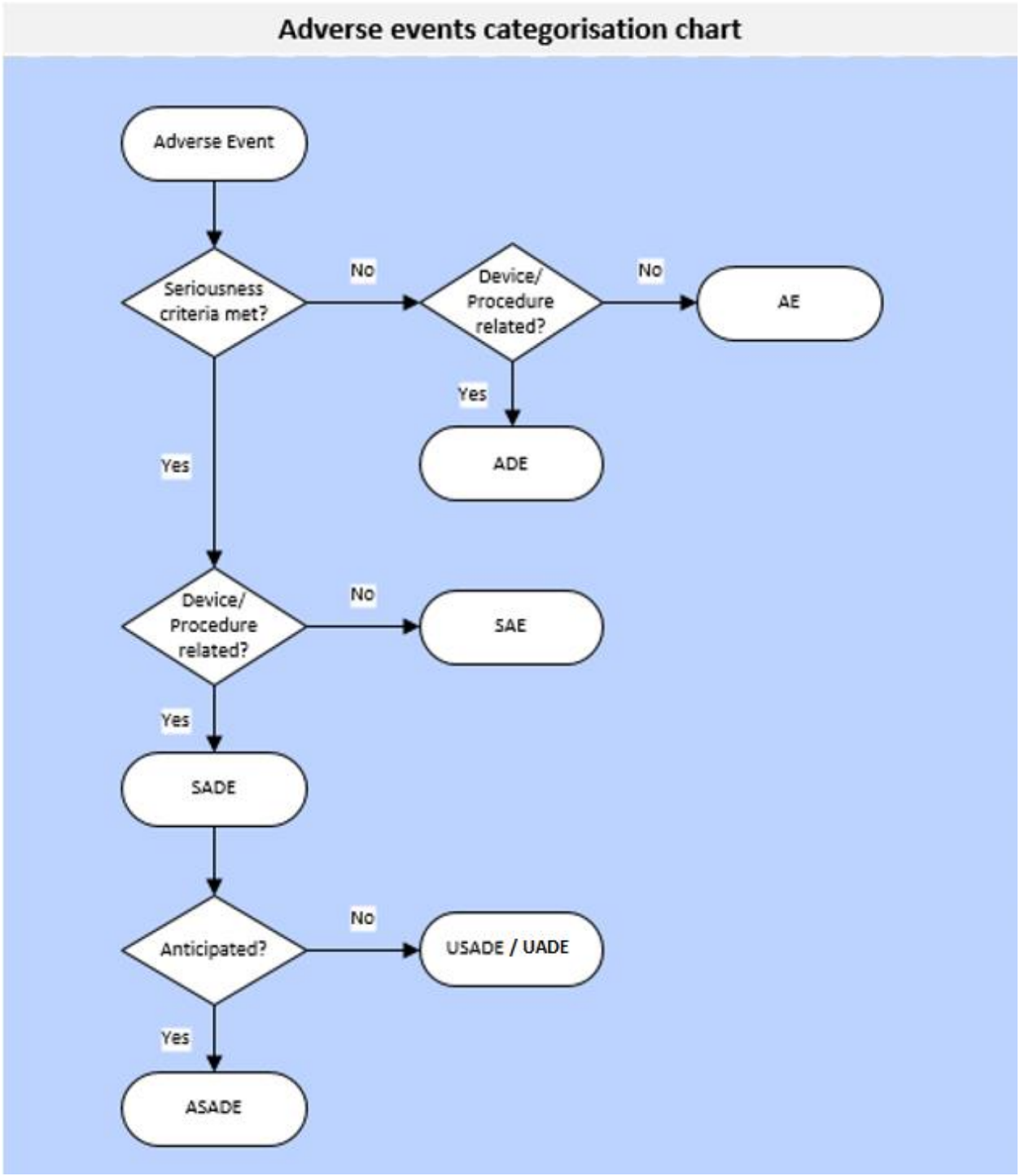
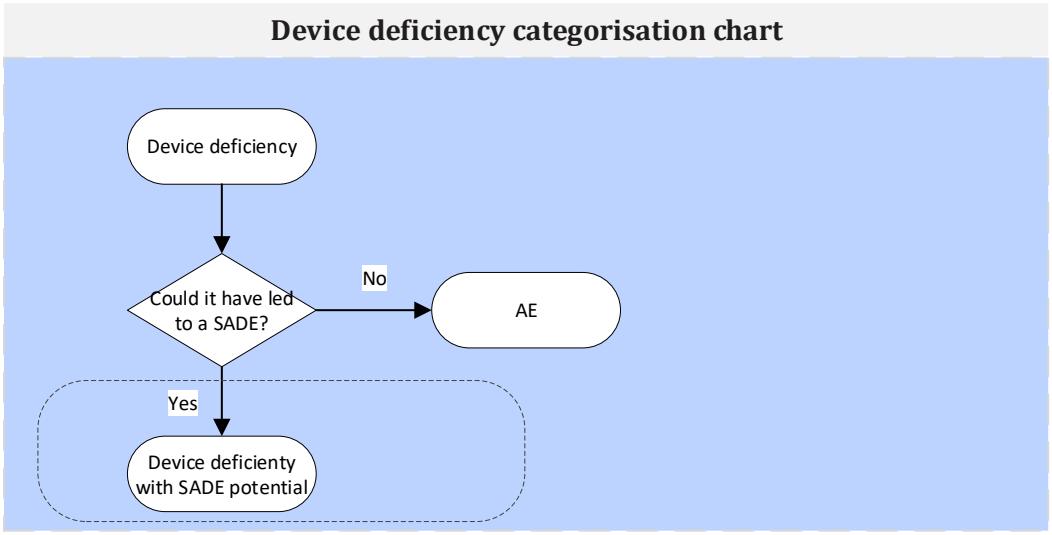


Figure 2: Device Deficiency Categorisation Chart



9.3 Observation, Categorization, Analysis and Reporting of AEs

AEs and DDs will be screened twice a day by VCLS VigOps and assessed during the clinical investigation by VCLS VigOps, the medical monitor as well as by a DSMB and classified in-line with the definitions of MDR, ISO 14155, IMDRF, MDCG and US specific definitions according to 21 CFR part 812.

All recorded and reported AEs and DDs will be reviewed by VCLS VigOps, Study Management and/ or designee. This review will include the determination whether the AE/DD meets regulatory reporting requirements (see Table 4: Adverse Event Reporting Requirements). The sponsor will ensure timely AE/DD reporting to meet global and country specific regulatory requirements.

A list of anticipated AEs that are expected in nature is included in Annex A of protocol–*" Clinical manifestations and medical occurrences, unintended diseases or injuries or clinical signs that are attributed to the concurrent illness / clinical condition of critically ill subjects in an ICU include"*.

In case the AE/DD is related to a Hamilton Medical market released device, other than the devices under study, used during the study, Hamilton Medical Study Management and/or designee will immediately report this device related AE/DD to the Hamilton Medical Vigilance (HMV) group. The HMV group will ensure prompt review, and appropriate reporting.

Hamilton will determine with the support of the Medical Monitor and DSMB members, on an ongoing basis if the risk assessment is to be updated and assess whether corrective or preventive action is required.

All AE´s that are contained in the **Annex A of protocol–*" Clinical manifestations and medical occurrences, unintended diseases or injuries or clinical signs that are attributed to the concurrent illness / clinical condition of critically ill subjects in an ICU include*"** can be classified as "anticipated", as these effects are

by their nature, incidence, severity and outcome previously identified in the risk assessment and the State-of-the-Art analysis. These events are common for the subject population intended and these events represent part of the natural outcome of this population with regard to the underlying diseases and the expected medical condition.

Attention will be paid for risks and AEs for the intended subject population (critically ill subjects requiring invasive mechanical ventilation) and the clinical background for the device in question identified from clinical experience for INTELLiVENT-ASV. Special attention will be paid to any potentially INTELLIVENT-ASV specific software issues, those events that can be attributed to the subject population on an ICU, but also can possibly be a typical, ventilation-related AE.

Figure 3: Adverse Event Review Chart

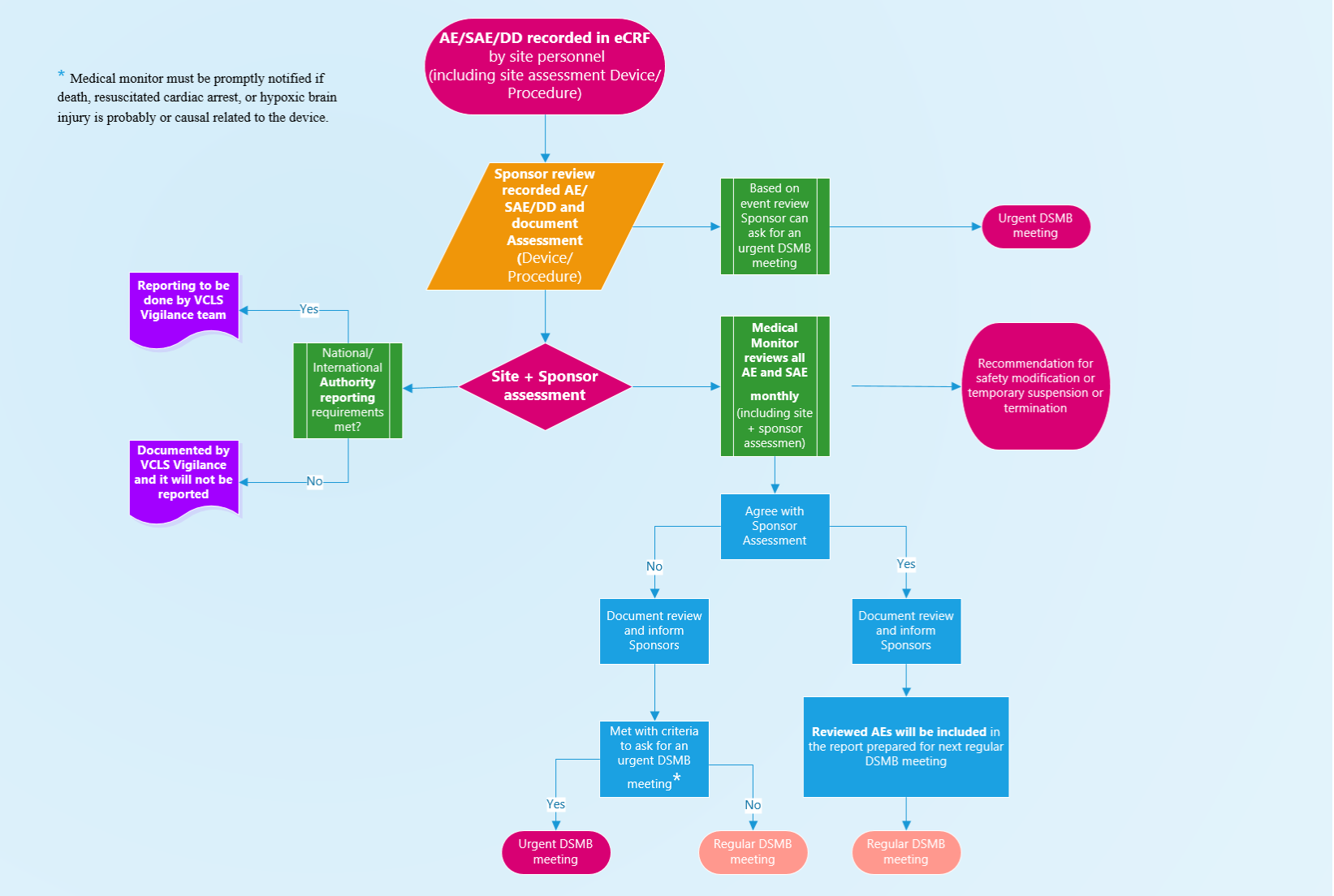

* Medical monitor must be promptly notified if death, resuscitated cardiac arrest, or hypoxic brain injury is probably or causal related to the device.
AE/SAE/DD recorded in eCRF by site personnel (including site assessment Device/ Procedure)
Sponsor review recorded AE/ SAE/DD and document Assessment (Device/ Procedure)
Based on event review Sponsor can ask for an urgent DSMB meeting
Urgent DSMB meeting
Reporting to be done by VCLS Vigilance team
Yes
National/ International Authority reporting requirements met?
Site + Sponsor assessment
Medical Monitor reviews all AE and SAE monthly (including site + sponsor assessmen)
Recommendation for safety modification or temporary suspension or termination
Documented by VCLS Vigilance and it will not be reported
No
Agree with Sponsor Assessment
No
Yes
Document review and inform Sponsors
Document review and inform Sponsors
Met with criteria to ask for an urgent DSMB meeting*
Reviewed AEs will be included in the report prepared for next regular DSMB meeting
Yes
No
Urgent DSMB meeting
Regular DSMB meeting
Regular DSMB meeting

Table 4: Adverse Event Reporting Requirements

SAEs, ADEs, SADEs, UADEs, USADEs and Device Deficiency with SADE potential:	
Investigator submit to:	
Hamilton Medical	As soon as possible, but in no case later than three (3) calendar days after the clinical site study team first learns of the event or of new information in relation with an already reported event.
EC/IRB	Reporting timeframe as per local EC/IRB requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.

All other AEs	
Investigator submit to:	
Hamilton Medical	Submit in a timely manner after the clinical site study team first learns of the event.
All other Device Deficiencies	
Investigator submit to:	
Hamilton Medical	Submit in a timely manner after the clinical site study team first learns of the deficiency.

9.3.1 Emergency contact details in case of AEs

In case of an immediately reportable AE the investigators can contact the Hamilton Medical Study Manager. Contact details of Hamilton Medical Study Management are given in the Investigational Site File.

In case the investigator requires information in a medical emergency situation the investigator can contact the Medical Expert. Contact details of Medical Experts are given in the Investigational Site File.

9.3.2 Analysis of the Benefit/Risk Profile

There will be periodically review and evaluation of the accumulated study data for safety, study conduct, progress and efficacy by Hamilton Medical and with the input of the Medical Monitor and DSMB.

Analysis of the Benefit/Risk Profile considers study specific data as well as relevant background knowledge about critically ill subjects, their medical diagnosis, treatment and prognosis and the investigational device.

It will be analyzed, if all risks and hazards are duly mitigated by risk management control procedures, and if additional information will be necessary to contribute to the benefit risk profile of the device.

10 STATISTICS

10.1 Statistical Hypothesis

EASiVENT hypothesizes that INTELLiVENT-ASV will outperform non-automated Ventilation on the Hamilton Medical Ventilators, in terms of efficacy and safety.

The hypothesis for the primary endpoint regarding effectiveness is that when all six variables are in the optimal target ranges, mechanical ventilation is optimized with a minimum risk of ventilation induced lung injury.

The hypothesis for the primary endpoint regarding safety is that that when one of these variables is in sub-optimal range, there is a risk of clinical complication, either ventilation induced lung injuries, or systemic complication.

10.2 Sample Size Determination

A minimum of 254 and maximum of 508 subjects will be included in this study, based on adaptive sample size assessments at scheduled interim analyses. Subjects will be selected for this study according to Section 7 of this protocol. Requirements related to participant withdrawal from the study are described in Section 7.6. All sites will have a minimum number of enrollment targets in order to meet overall cross-site enrollment and protocol goals.

Inclusion will be halted at sites that reach the 30% inclusion cap of total enrollment.

Sample sizes for a group sequential design with 2 interim analyses

The planned sample size is a minimum of 254 and a maximum of 508 subjects.

The sample sizes for this trial are calculated using the following assumptions:

- significance level equal to 0.025 (1-sided)
- power of 0.8 (at final analysis)
- allocation ratio of 1:1
- Two interim analyses at half and three-quarter information time (i.e. when half and three-quarter of the subjects are evaluable for response), spending functions with O'Brien-Fleming-Type boundaries for efficacy and futility. Efficacy endpoint (%All in optimal, more is better) on logit-scale:
    - Mean conventional = -1.86
    - Mean INTELLiVENT-ASV = -1.28
    - Sd = 1.5 for both devices
- Safety endpoint (%Any in sub-optimal, less is better) on logit-scale:
    - Mean conventional = -0.09
    - Mean INTELLiVENT-ASV = -0.74
    - Sd = 1.6 for both devices

- Correlation between endpoints = -0.85
- Dropout could occur when subjects are ventilated for less than 24 hours after inclusion because of unexpected death, transfer to another ICU or withdrawal of informed consent. A maximum dropout rate of 5% of these cases is expected. Given that the large uncertainty on the assumed performance differences and the inclusion of a sample size reassessment, the initial sample size is not increased to deal with this dropout rate. At the second interim the sample size will be re-estimated, taking this observed dropout rate into account.

The table below shows the sample sizes and characteristics of a study with two (2) interim analyses, with O'Brien-Flemming boundaries for efficacy and futility. The final sample size for this group sequential design is 254. 254 stands for the number of subjects with evaluable endpoints and means more subjects might have to be enrolled to reach this number. The p-values for significance are increasing at each analysis while the p-value to stop for futility decreases from the first interim analysis to the final analysis. The study has a high probability to stop at the first interim analysis if both ventilation modes have an equal performance.

Table 5: Sample sizes and operational characteristics for the trial using O'Brien Fleming boundaries for futility and efficacy.

Analysis	SS	Z Efficacy	Nominal p Efficacy	α Spend	Power (Prob stop H_A)
1 (IA1)	128	2.96	0.0015	0.0015	0.25
2 (IA2)	192	2.36	0.0093	0.0097	0.43
3 (final)	254	2.02	0.0220	0.0250	0.19

Analysis	SS	Z Futility	Nominal p Futility	Prob Futility Stop (Prob stop under H_0)
1 (IA1)	128	0.44	0.3315	0.67
2 (IA2)	192	1.34	0.0904	0.25
3 (final)	254	2.02	0.0220	0.06

Recorded data has to be 24 h at minimum, and 80% of the invasive ventilation duration within the allocated randomized ventilation mode have to be recorded in the Memory box.

10.3 Adaptive sample size increase

An adaptive sample size reassessment is foreseen at the second interim analysis. In case promising results are obtained at this interim analysis, additional resources will be committed to the trial. Following Metha and Pocock (1), sample sizes will only be increased in case the interim results are promising, in which case the overall type-I error is not inflated by use of the conventional Wald Statistic. The maximum number of additional subjects will be capped at 254 (above the pre-planned 254 subjects) or a maximal total sample size of 508. In addition, following Chen, DeMets and Lan (33) and Gao, Ware and Mehta (34), sample sizes will only be increased in case the interim results are promising, in which case the type-I error is not inflated by use of the conventional Wald statistic. More specifically, this 'promising zone' is defined in terms of the conditional probability of rejecting the null-hypothesis at final analysis, given the estimated performance difference at interim ('conditional power') and assuming that this estimated performance difference is the true underlying difference. Depending on the conditional power (CP) for each of the two endpoints at the second interim analysis, we consider three different zones and anticipated actions:

1) **Unfavorable zone**: At least one endpoint with CP <0.33.

The interim results are so disappointing that it is not worth to increase the sample size to retrieve CP and the original sample size is retained. Following (34), this zone is defined as 0 to 0.33, for a sample size reassessment at 0.75 information fraction and a maximal increase in sample size of 50%. If the CP for either of endpoints is below 0.33, this is considered unfavorable and no sample size increase will be performed.

2) **Promising zone**: Both endpoints with CP >0.33, at least one endpoint with CP <0.80

If the CP is above 0.33 but below the originally planned 0.80 for at least one endpoint, the sample size will be increased by just the right amount to recover the targeted power of 0.80, while not exceeding the pre-specified maximal sample size of 508 subjects. As stated above, both endpoints would need to have a CP above 0.33 and one endpoint a CP below 0.80 to embark on a sample size increase. The sample size increase will be set to the higher of two recalculated sample sizes if both endpoints have a CP between 0.33 and 0.80.

3) **Favorable zone**: Both endpoints CP >0.80

The conditional power at second interim analysis is 0.80 or larger for both endpoints. In this zone, the interim results are sufficiently favorable that the trial continues to the original sample size without the need to adaptively increase the trial size.

10.4 Statistical Analyses

10.4.1 Definition of populations

The following populations will be used:

10.4.2 Intention-To-Treat (ITT) Population

The Intention-To-Treat population (ITT) will consist of all randomized subjects, whether they receive invasive (mechanical or non-mechanical) ventilation. Subjects who receive the wrong ventilation support will be analysed in the arm to which they were randomized. The ITT population will be used for primary efficacy analyses.

10.4.3 Modified Intention-To-Treat (MITT) Population

The MITT population consists of all ITT subjects whose recorded data are at least 24h and at least 80% of the invasive ventilation duration within the allocated randomized ventilation mode is recorded in the eCRF The sensitivity analyses for efficacy endpoints will be conducted using the MITT population. Subjects will be analyzed in the group to which they were randomized.

10.4.4 Safety Analysis Population

The Safety population will include all subjects who once received invasive (mechanical or non-mechanical) ventilation. Subjects will be analyzed according to the treatment that they actually received. The safety population will be used for safety analyses.

10.4.5 Analysis of Primary Endpoints

The objective of this study is to compare the efficacy and the safety of the investigational automated ventilation (INTELLiVENT-ASV) with a control ventilation group (conventional non-automated ventilation) in ICU subjects.

The hypothesis is that INTELLiVENT-ASV is better than conventional non-automated ventilation in terms of efficacy and safety.

Efficacy and safety endpoints are composite endpoints and are based on six variables that will be continuously recorded during the study period:

1) Tidal volume (VT)
2) Maximum pressure (Pmax)
3) Oxygen saturation measured by pulse oximetry (SpO2)
4) End-tidal partial pressure of carbon dioxide (PetCO2)
5) Respiratory rate (RR) for spontaneous breathing subjects
6) Pmax-PEEP for passive ARDS subjects

Endpoints will be measured up to seven (7) days after randomization

Values for optimal, acceptable and sub-optimal ranges have been defined according to previously published studies (13, 14) and current recommendations. These ranges are adapted to the subject clinical condition and may be different for passive and spontaneous breathing ventilation periods.

Table 6: Values for optimal, acceptable and sub-optimal ranges

Variable	Ref.	Subject condition	Subject activity	Sub-optimal low	Acceptable low	Optimal	Acceptable high	Sub-optimal high
SpO2 (%)	20	None	Passive or active	< 90	≥90 and <94	≥94 and ≤98 Or > 98 if FiO2= 21%	> 98	NA
SpO2 (%)		ARDS	Passive or active	< 85	≥85 and <88	≥88 and ≤96 or > 96 if FiO2= 21%	>96	NA
SpO2 (%)	20	Brain injury	Passive or active	< 90	≥90 and <94	≥94 and ≤98 Or > 98 if FiO2= 21%	> 98	NA
SpO2 (%)	20	Chronic hypercapnia	Passive or active	< 85	≥85 and <88	≥88 and ≤92 or > 92 if FiO2= 21%	>92 and ≤98	> 98
PetCO2 (mm Hg)		None	Passive	< 25	≥ 25 and < 34	≥ 34 and ≤ 44	> 44 and ≤49	> 49
PetCO2 (mm Hg)	19	ARDS	Passive	< 25	≥ 25 and < 32	≥ 32 and ≤ 42	> 42 and ≤ 52	> 52
PetCO2 (mm Hg)		None or ARDS	Active	NA	< 25	≥ 25 and ≤45	> 45 and ≤55	> 55
PetCO2 (mm Hg)		Brain injury	Passive or active	< 29	≥ 29 and < 34	≥ 34 and ≤ 39	> 39 and ≤ 44	> 44
PetCO2 (mm Hg)		Chronic hypercapnia	Passive or active	< 25	≥ 25 and < 35	≥ 35 and ≤ 55	> 55 and ≤ 60	> 60
VT (mL/Kg IBW)	21	None	Passive	< 4	≥ 4 and < 5	≥ 5 and ≤ 8	> 8 and ≤ 10	> 10
VT (mL/Kg IBW)	15, 27, 35	ARDS	Passive	< 4		≥ 4 and ≤ 8	> 8 and ≤ 10	> 10
VT (mL/Kg IBW)		None,ARDS, or brain injury	Active	< 4	≥ 4 and < 5	≥ 5 and ≤ 10	> 10 and ≤ 12	> 12
VT (mL/Kg IBW)		Brain injury	Passive	< 4	≥ 4 and < 5	≥ 5 and ≤ 8	> 8 and ≤ 10	> 10
VT (mL/Kg IBW)		Chronic hypercapnia	Passive or active	< 4	≥ 4 and < 5	≥ 5 and ≤ 10	> 10 and ≤ 12	> 12
Pmax (cm H2O)		None	Passive	NA	< 10	≥ 10 and ≤ 25	> 25 and ≤ 30	> 30
Pmax (cm H2O)	15, 27, 35	ARDS	Passive	NA	< 10	≥ 10 and ≤ 30	> 30 and ≤ 35	> 35
Pmax (cm H2O)		None or ARDS	Active	NA	< 10	≥ 10 and ≤ 25	> 25 and ≤ 30	> 30
Pmax (cm H2O)		Brain injury	Passive or active	NA	< 10	≥ 10 and ≤ 25	> 25 and ≤ 30	> 30
Pmax (cm H2O)		Chronic hypercapnia	Passive or active	NA	< 10	≥ 10 and ≤ 30	> 30 and ≤ 35	> 35
Pmax-PEEP (cm H2O)	4,	ARDS	Passive	NA	NA	<15	≥15 and <18	≥ 18
RR (b/min)		None	Active	< 10	≥ 10 and < 12	≥ 12 and ≤ 30	> 30 and ≤ 35	> 35
RR (b/min)		Brain injury or ARDS	Active	< 10	≥ 10 and < 12	≥ 12 and ≤ 35	> 35 and ≤ 40	> 40
RR (b/min)		Chronic hypercapnia	Active	< 8	≥ 8 and < 10	≥ 10 and ≤ 35	> 35 and ≤ 40	> 40

Efficacy and safety endpoints are co-primary endpoints:
Efficacy will be calculated as the percentage of time spent with all variables in the optimal target ranges.
Safety will be calculated as the percentage of time spent with at least one variable in the sub-optimal target ranges.

10.4.6 Baseline Descriptive Characteristics

All subjects' characteristics at baseline will be described overall and by treatment group:

- Age,
- Height and weight,
- Comorbidities and medical history,
- Treatment concomitant,
- Reason for hospitalization
- Smoking status
- Ethnicity, if possible

10.5 Missing Data

Please refer to section 7.2 "Inclusion Criteria" and 8.4 "End of study".

Subject will be considered to have completed the study for the following reasons:

- Subject completes follow-ups (Day 28) required per investigational plan.
- Subject dies.
- Subject or legally authorized representative requests to be withdrawn from the study.
- Investigator requests to be withdrawn from the study to protect the welfare of the subject. (In that case, it is at the site's principal investigator's discretion to determine that the study is no longer in the subject's best interest).

The sponsor deems a dataset "complete" if both of the following conditions are achieved:

1. Minimum of 24h of recorded data available
2. Minimum of 80% of the total invasive ventilation within the allocated randomized ventilation mode time has been recorded.

An incomplete dataset leading to a dropout in the study is a dataset that misses at least one of the above mentioned variables.

The reason for an incomplete dataset can be:

- Early termination of recording caused by a transfer to another ICU
- Subject or legally authorized representative requests to be withdrawn from the study.
- Site's Principal Investigator's decides to stop the inclusion for any reason.
- Technical failure in recording.
- Less than 80% the invasive ventilation within the allocated randomized ventilation mode duration have been recorded in the Memory Box.
- Recorded data is less than 24h.

Dropout could occur when patients are ventilated for less than 24 hours after inclusion because of: unexpected death, transfer to another ICU, or withdrawal of informed consent. We expect a maximum of 5% of these cases.

Note a maximum of 5% of subjects are anticipated for which not 80% of mechanical ventilation time within the allocated randomized ventilation mode could be recorded due to documented technical reason. The recorded data will be used (with 'percent spent' calculated per the recorded time) for the primary analysis of the co-primary endpoints. As a sensitivity analysis, these values will be treated as missing data.

Because technical failure in recording may not be detected on time by the investigators, a continued enrollment is planned.

Technical issue in capturing the necessary data, the dropout probability is assumed to be equal for all subjects, regardless of their condition and ventilation modalities. Therefore, replacing subjects without collected data is not expected to cause any bias.

It is assumed the study will enroll subjects until the required number of subjects with evaluable endpoints has been reached.

11 QUALITY ASSURANCE AND CONTROL

11.1 Data handling

11.1.1 Case Report Forms

As used in the protocol, the term Case Report Form (CRF) should be understood to refer to an electronic data record.

A CRF is required and should be completed for each enrolled subject. The completed original CRF is the sole property of Hamilton Medical and should not be made available in any form to third parties, except for authorized representatives of Hamilton Medical or appropriate regulatory authorities, without written permission from Hamilton Medical.

The investigator has the ultimate responsibility for the collection and reporting of all data entered in the CRF and ensuring that they are accurate, authentic, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

The CRF should be electronically signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (as necessary) and should not obscure the initial data.

11.1.2 Specification of source documents

Source Documents and Access to Source Data/Documents:

All sites must maintain source data/documents in accordance with ISO 14155:2020. Each site will maintain, and store securely, complete, accurate and current study records throughout the study. The sites will maintain all study documentation for a minimum of two years following the date of marketing approval for the device being tested for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two year after the investigation is discontinued and the US FDA is notified. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

Source documents are the hospitals or the physician's subject chart and data collected automatically from the ventilator. Data collected automatically from the ventilator will not be monitored. They will be extracted from the ventilator and directly integrated to the database.

In some cases the CRF, or part of the CRF, may also serve as source document. In these cases, a document should be available at the investigator's site as well as at Hamilton Medical to clearly identify those data recorded in the CRF and for which the CRF will stand as source document.

11.1.3 Record keeping / archiving

Study records must be maintained on site for the entire period of study implementation. Instructions for record storage will be provided by Hamilton Medical. The records should be retained by the investigator according to ICH, ISO14155:2020 and local regulations or as specified in the clinical study agreement, whichever is longer.

No study records may be moved to an off-site location or destroyed prior to receiving approval from Hamilton Medical. If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g. retirement, relocation) Hamilton Medical should be prospectively notified. The study records must be transferred to a designee acceptable to Hamilton Medical such as another investigator, another institution, or to an independent third party arranged by Hamilton Medical. The investigator must obtain Hamilton Medical written permission before disposing of any records, even if retention requirements have been met.

11.2 Data management

11.2.1 Data Management Responsibilities

Study CRFs will be developed by the data manager and statistician in conjunction with Hamilton Medical. Quality control reports and queries will be routinely generated and distributed automatically by the eCRF to the study sites for verification and resolution. As part of the study activation process, the study site must identify all CRFs or part of the CRFs to be used as source documents.

Subject's ventilation data in both arms are directly recorded from the ventilators via a serial port using a Memory Box. The Memory Boxes are compatible with all Hamilton Medical ventilators.

This memory box contains a memory card and is solely for investigational use and is just basically saving output data from the ventilators. These data will not be cleaned due to the automated nature of the subject recordings.

11.2.2 Data Management System

The Data Management System is an electronic system hosted by the CRO, Soladis.

11.2.3 Data Safety

Data Management activities are managed by a CRO, Soladis.

The Data Entry application (EDC) is created by the Soladis developer's team. The outputs are validated and reviewed by the Soladis Data Manager.

11.2.4 Analysis and archiving

At the end of the project, the data entered in the EDC (audit trial included) of each site are transmitted to the latter as PDF prints of the CRF (archival copies) stored by subject on CD-ROM/DVD-Rom.

The eCRFs data (PDF file), appendices, documents and study specific quality records which constitute the Data Management part of the Trial Master File are filed in binders, labelled and transmitted to Hamilton Medical according to the instructions. Remaining copies are destroyed. Once the statistical analysis is completed, or before on Hamilton Medical's demand, the database is archived on CD-Rom/DVD-Rom and removed from Soladis database.

11.2.5 Electronic and central data validation

Proper data recording will be monitored by dedicated study CRAs. Monitoring activities and checks to be performed before the transfer to central database are defined in the monitoring plan.

Ventilation parameters recorded by breath and by subject will be recorded on a SD card inserted in the Memory box. Data saved on the SD card will be transferred from participating sites in an anonymized form, and then stored on secure servers within Soladis. Any subject related documents will not be transferred to any unauthorized party and are will not be processed and/or transferred other than in accordance with the subjects' consent.

All baseline, follow up data will be entered on an eCRF. Information on the eCRF will, where relevant, be accepted as source data and transferred, in part, and as appropriate, to a database, password protected to defined users and with an audit trial managed from Soladis.

11.3 Monitoring Plan

A site qualification visit may be conducted by Sponsor (or designees) to review the clinical investigational plan, regulatory and study requirements with the investigator and study personnel.

A site initiation visit will be performed once regulatory approvals are obtained and the site's requirements for study participation are met. Sites will be considered as active once training phase is completed for US sites.

Source data review will be carried out by a Clinical Research Associate (CRA), a representative of the Sponsor who will conduct on-site visits to check the CRF data against the original documents and confirm that these are complete and clear.

The CRA will ensure that the study is conducted in accordance with the protocol and with regulatory requirements by frequent communications (by letter, telephone or fax) and that subjects' rights are respected.

The study closure visit will be performed by the monitor at the end of the study.

A monitoring plan is detailing all monitoring procedures.

11.4 Quality Assurance, audits and inspections

The monitoring and audit procedures written by Hamilton Medical will be set up in order to be consistent with Good Clinical Practice and ISO 14155:2020. Direct on-site access to the site's documentation and medical records must be permitted.

In order to guarantee that the clinical study protocol complies with Good Clinical Practice, ISO 14155: 2020 and current regulatory requirements, the investigator must allow audits to be performed by, or at the request of Hamilton Medical or by people instructed by Hamilton Medical, and inspections to be carried out by the Competent Authorities.

The investigator undertakes to grant the auditors/inspectors direct access to examine the study records in knowledge of the fact that these people are subject to professional secrecy and that as such they must not reveal either the identity of people or their medical information.

The investigator undertakes to assist in the correct conduct of audits and inspections as well as possible, enabling access to all of the premises, data and documents required. The medical file and any other study documents may be photocopied during an audit or inspection provided that the names of the subjects are blanked out on the copies in order to guarantee confidentiality.

As soon as the investigator is informed of a forthcoming inspection by the authorities, he/she will inform Hamilton Medical and allow Hamilton Medical to take part in this inspection.

During these inspections, the confidentiality of the data checked and subject protection must be observed.

The investigator will communicate all of the results and all of the information resulting from the inspections carried out by the regulatory authorities to Hamilton Medical as soon as possible.

The investigator will take the appropriate measures as instructed by Hamilton Medical to rectify any problems identified during the audit or during the inspections. A site visit log will be maintained at study site to document all visits.

11.5 Study management

The study is sponsored by Hamilton Medical.

Study team contact details will be provided in the investigational site file as part of the Trial Master File.

11.6 Records and reports

11.6.1 Study Investigator records

An Investigator Site File will be maintained up to date by the investigator.

At a minimum, the following records must be kept up to date by the study site:

- Clinical Investigation Plan and, if applicable, any amendments with signed page
- IRB/EC correspondence, including approvals
- Instructions for Use
- IRB/EC approved Informed Consent form

- Regulatory Authority approval or notification
- Fully signed Clinical Investigation Agreement and confidentiality agreement (if not included in the Clinical Investigation Agreement)
- Financial disclosures
- Completed Delegation of Authority Form and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications from sponsor, monitor
- Subject screening log and/or subject identification log
- Signed, dated and fully executed Informed Consent forms
- Fully executed CRFs and corrections
- Reports of Adverse Events and Device Deficiencies
- Device accountability records, if required

11.6.2 Investigator reporting responsibilities

Table 7: Investigator Reporting Responsibilities

Report	Submitted to	Description
Unanticipated Adverse Device Effect	EC/IRB and Sponsor	Refer to Table for Adverse Event Reporting Requirements (above)
Adverse Events	Sponsor	Refer to Table for Adverse Event Reporting Requirements (above)
Withdrawal of EC/IRB approval	Sponsor	US: An investigator shall report to the sponsor, within five (5) working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. (21 CFR 812.150(a)(2)). Europe: As required and in compliance with local regulatory requirements.

Report	Submitted to	Description
Progress	Sponsor, the monitor, and the EC/IRB	US: An investigator shall submit progress reports on the investigation at regular intervals, but in no event less often than yearly. (21 CFR 812.150(a)(3)). Europe: As required and in compliance with local regulatory requirements.
Study deviations	Sponsor and EC/IRB	US: Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (21 CFR 812.150(a)(4)). Europe: As required and in compliance with local regulatory requirements.
Failure to obtain Informed Consent prior to investigational device use	Sponsor and EC/IRB	US: If an investigator uses an investigational device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5)). Europe: As required and in compliance with local regulatory requirements.
Final Clinical study report	Sponsor, EC/IRBs and Relevant Authorities	US: This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. (21 CFR 812.150(a)(6)). Europe: As required and in compliance with local regulatory requirements.

Report	Submitted to	Description
Other	EC/IRB and FDA	US: An investigator shall, upon request by a reviewing EC/IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 12.150(a)(7)). Europe: As required and in compliance with local regulatory requirements.

11.6.3 Hamilton Medical records

At a minimum, the sponsor will keep the following records in the Trial Master File:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Instructions for Use
- Sample of labeling attached to the investigational device
- Curriculum Vitae of investigators and investigation site personnel
- Delegation of Authority Form and training records of investigators and investigation site personnel
- EC/IRB approvals/notifications and regulatory approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Shipping records for investigational devices and clinical-investigation related documents and materials, if required
- EC/IRB approved Informed Consent Forms
- Site selection reports, site initiation reports and monitoring visit reports
- Adverse event and Device Deficiency reports
- Financial disclosure information
- Fully executed CRFs and corrections

11.6.4 Hamilton Medical reporting requirements in US

Table 8: Hamilton Medical Reporting Requirements in Us

Report	Submit to	Description
Adverse Events	IRB, Investigators, FDA and relevant authorities, where applicable	Sponsor will report adverse events as required and in compliance with local regulatory requirements, as applicable and described in Study Medical Device Vigilance and Project Specific Procedure Plan
Unanticipated Adverse Device Effect (UADE)	Investigators, IRB, FDA, and relevant authorities	Notification within ten (10) working days after the sponsor first receives notice of the effect. *(21 CFR 812.150(b)(1)).*
Withdrawal of IRB approval	Investigators, IRB, FDA, and relevant authorities	Notification within five (5) working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2)).*
Withdrawal of FDA approval	Investigators, IRB, and relevant authorities	Notification within five (5) working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3)).*
Current Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4)).*
Progress Reports	IRB and FDA	At regular intervals, but not less than yearly, a sponsor shall submit progress reports to all reviewing IRB's and EC's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with § 812.36(f) and annual reports in accordance with this section.
Recall and device disposition	IRB relevant authorities, and FDA	Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6)).*
Failure to obtain Informed Consent	FDA	Investigator's report will be submitted to FDA within five (5) working days of notification. *(21 CFR 812.150(b)(8)).*

Report	Submit to	Description
Other	IRB/FDA	Sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10)).

11.6.5 Hamilton Medical reporting requirements in US /EU

Report	Submit to	Description
Adverse Events, Device Deficiencies	EC, Investigators, and relevant authorities, where applicable	Sponsor will report adverse events as required and in compliance with local regulatory requirements, as applicable and described in Study Medical Device Vigilance and Project Specific Procedure Plan
Premature termination or suspension of study	Investigators,EC/ IRB, and Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(*ISO 14155: 2020*), (MHLW Ordinance 36, Article 32).*
Final Report	Investigators, EC IRB, and regulatory authorities, where applicable and FDA	Sponsor will notify EC/IRB and FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and EC/IRBs within six (6) months after completion or termination of this study. (21 CFR 812.150(b)(7)). In Europe – per the local laws and regulations.
Study Deviations	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation and reported per local laws and regulations.

11.7 Subject compensation and indemnification

Subjects will not receive any compensation for their participation in this study.

11.8 Confidentiality, Data Protection

Any confidential information relating to INTELLIVENT-ASV or the study, including any data and results from the study will be the exclusive property of Hamilton Medical. The investigator and any other persons involved in the study will protect the confidentiality of the proprietary information belonging to Hamilton Medical.

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

11.9 Amendments to the CIP

Any change to this protocol will be documented in a protocol amendment, issued by Hamilton Medical, and agreed upon by the principal investigator prior to its implementation. Protocol Amendments and documents updated as a result of the Protocol Amendment must not be implemented until all approvals (EC/IRB and RAs, if applicable) have been obtained.

Changes to the protocol to eliminate immediate hazard(s) to study subjects may be implemented prior to EC(s)/IRB(s) and RA approval.

11.10 Deviations from the Clinical Investigation Plan

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the clinical investigational plan, applicable laws or regulations, or the Investigator Agreement.

Under working conditions, deviations from the protocol may occur. Every attempt must be made to avoid deviations. All deviations will be recorded for the study.
United States regulations (21 CFR 812.140) require that investigators maintain accurate, complete, and current records relating to the clinical study. This includes documents showing the dates and reasons for each deviation from the clinical investigational plan.
If deviations from the protocol are reported, the investigator informs the monitor, and the implications of the deviation needs be escalated to Hamilton Medical.
All protocol deviations must be reported to the EC/IRB policies and/or local laws, as applicable. All deviations will be summarized and reported in regular progress reports to the FDA. Deviation reports and supporting documentation will be kept in the investigator site file and the study master file.

11.10.1 Request for approval of study deviations

In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and Regulatory Authority must also be obtained

before implementation. The investigator shall timely contact the monitor and Hamilton Medical for review of the proposed change/deviation.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. The investigator shall report the deviation as soon as possible to Hamilton Medical and the reviewing EC/IRB, if applicable. Hamilton Medical will inform the Regulatory Authorities, if required.

11.10.2 Reporting requirements for study deviations

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

Hamilton Medical is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the protocol, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study:

- Non-compliance to obtain subject's informed consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow subjects per scheduled follow-ups
- Failure to submit data in a timely manner
- Failure to follow-up with findings on monitoring reports
- EC/IRB approval expiration
- EC/IRB suspension of the center

If a site is terminated or suspended, no additional enrollments will be allowed at the center.

Hamilton Medical will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

12 Study device/product traceability

12.1 Supply of investigational devices/products

Hamilton Medical investigational devices/products will be ordered and shipped to the site prior site activation as applicable. All devices are supplied with INTELLIVENT-ASV Software accessory.

However, the activation of the INTELLiVENT-ASV software accessory can be done only with a key code provided by the sponsor.

US only: The investigational device (INTELLiVENT-ASV accessory is activated), the instructions for use, or the packaging, or the ventilator will indicate that the investigational device is exclusively for use in a clinical investigation.

12.2 Storage and handling of investigational devices/products

US only: Investigational devices/products must be stored in a secured area if they are not used to treat study patients. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this clinical investigation plan. In addition, all information for the use, storage, and handling of the investigational device/product as indicated in the Instructions for Use must be taken into account.

12.3 Device return procedures

All non-functioning devices/products should be returned to Hamilton Medical for analysis.

The final disposition of the device must be recorded on the device disposition log, if the device is Hamilton's property. Relevant information should also be recorded on associated eCRF. Detailed instructions for the return of non-functioning devices will be provided in the investigational site file.

13 PUBLICATION POLICY

It is understood that this study is part of a multi-center study and a publication of data/results from all sites is expected. Hamilton Medical certifies that it intends to submit the multicenter study results for publication in a peer-reviewed medical journal and/or to submit such results for disclosure in a publicly accessible website within twelve (12) months after the study conclusion. If the study results are under review by peer-reviewed medical journals that prohibit pre-publication disclosure at the 12-month timeframe, Hamilton Medical agrees that disclosure will be posted on publicly accessible websites at the time of publication. The study results will be disclosed as soon as possible if there are any significant safety findings. Hamilton Medical further certifies that the multicenter study results will be published/disclosed regardless of whether they support the hypothesis being tested or are contrary to the predicated outcome. At such time as the results are submitted for publication or posted on publicly accessible websites at the time of publication, notification that a submission of the multi-center results is not planned, or eighteen (18) months after the study conclusion, whichever shall first occur, Hamilton Medical shall make study results available to the investigators for individual publication analysis and public disclosure. Investigators shall be free to publish the data/results from the study in accordance with this section. Investigators shall be free to publish the data/results of the Study subjects agreed in the contract with Hamilton Medical.

The Institution shall require the investigators to furnish Hamilton Medical with a copy of any proposed publication prior to submission for publication, at least sixty (60) days prior to submission for manuscripts and at least twenty-one (21) days prior to submission for abstracts. Hamilton Medical shall be entitled to review such proposed publications solely for the purpose of identifying Hamilton Medical's confidential information, which shall be removed from the publication upon Hamilton Medical's request to the extent such deletion does not preclude the complete and accurate presentation and interpretation of the study results; and to identify any patentable inventions, which shall be addressed as described below; and to provide any other comments Hamilton Medical desires to provide, provided that investigators shall have no obligation to address any such additional comments.

At the expiration of such sixty (60) day or twenty-one (21) day period, investigators may proceed with submission for publication provided that any identified Hamilton Medical's Proprietary Information has been removed; and provided further that upon notice by Hamilton Medical that Hamilton Medical reasonably believes a patent application claiming an Invention should be filed prior to such publication, in Institution's discretion such submission shall be delayed for up to an additional sixty (60) days or until any patent application or applications have been filed, whichever shall first occur. In no event shall the submission of such publication of results be delayed for more than one hundred and twenty (120) days for manuscripts and for more than sixty-seven (67) days for abstracts from the date such proposed publication was provided to Hamilton Medical; at the end of said one hundred and twenty (120) or sixty-seven (67) days, investigators shall be free to publish such results as proposed.

If an investigator is or becomes the multi-site coordinating principal investigator or overall Study chair, he/she shall have access to data from all Study sites for analyses for publication. If an investigator is or becomes an author or if the investigator's activities warrant authorship on any multi-center Study publication, or if the investigator is or becomes a member of any Study publication and analysis

committee, the investigator shall have access to data from all Study sites for analyses for publication. Hamilton Medical shall also provide the Investigator in any of these events with a copy of the abstract and manuscript for any multi-center Study publication and with an adequate opportunity to review and have input into such abstract and manuscript prior to submission for publication. The investigator shall, in all cases, at his/her sole discretion, have the right to decline to be an author and to have his/her name removed as an author from any multi-center Study publication.

If Hamilton Medical chooses to provide publication support for any multicenter publication that includes the investigator as an author, such support shall be governed by an Agreement between the investigator and Hamilton Medical, including but not limited to its publication provisions. For the purpose of clarity, any such publication support is a transfer of value between Hamilton Medical and Institution and not to the investigator for purposes of reporting under The Physician's Payment Sunshine Act.

If no multi-center Study publication occurs within twelve (12) months after the Study Conclusion, Hamilton Medical shall at that time provide access to data from all Study sites to the Study academic coordinating site, or if Hamilton Medical elects not to provide access to data from all Study sites to the Study academic coordinating site, then upon request it will provide access to data from all Study sites to Institution or to at least one other academic medical center participating in the Study for purposes of publication of the Study results.

14 FUNDING AND SUPPORT

This study is funded and supported by Hamilton Medical AG and local sponsor Hamilton Medical Inc.

15 INSURANCE

The sponsor will cover the study by a subject-insurance.

Hamilton Medical Inc. is a wholly owned subsidiary of Hamilton Medical AG., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB.

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Annex A: Identification of Risks and AE´s for the intended subject population, the clinical background and the device in question identified from clinical experience for INTELLiVENT-ASV

State of the Art: Adverse Events for mechanical ventilation and critically ill ICU population

A sound review of documentation for the medical fields of mechanical ventilation has been conducted. Applicable medical standards and guidance documents (published by medical associations) describe the natural course of critically ill subjects and the consequences of mechanical ventilation.

As the more common indications for invasive mechanical ventilation are inability to protect the airway, inadequate oxygenation and inadequate ventilation, Risks and Adverse events for Mechanical Ventilation overlap with conditions of the underlying disease that were reasons for the admission to an ICU.

In a population-based study of 8,309,344 US cases of non-surgical episodes of invasive mechanical ventilation, hospital mortality was strongly influenced by the underlying medical diagnosis. In 2009, hospital mortality amounted to 34.2% for pneumonia, 18.5% for COPD and 32.7% for heart failure subjects requiring invasive mechanical ventilation [2].

Root causes for mechanical ventilation of critically ill subjects in an ICU (industrialized countries) are:

Table 9: Root causes for Mechanical Ventilation [3]

Root causes for Mechanical Ventilation	Occurence
COPD	5%
Asthma	1%
Other chronic lung diseases	2%
Coma	19%
Neuromuscolar diseases	1%
Acute respiratory failure	
Postoperative	21%

2 A B Mehta, SN Syeda, RS Wiener, AJ Walkey Epidemiological Trends in Invasive Mechanical Ventilation in the United States: A Population-Based Study J Crit Care. 2015 Dec; 30(6): 1217–1221.

3 Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016 Feb 23;315(8):788-800.

Pneumonia	11%
Sepsis	9%
ARDS	3%
Congestive Heart failure	6%
Cardiac Arrest	5%
Trauma	6%
Aspiration	3%
Other	9%

Characteristics and outcome for ventilated ICU subjects **(industrialized countries)**

Table 10: Characteristics and outcome for ventilated ICU subjects [4]

Endpoint	Occurrence in %
Death of ventilated ARDS subjects	27-45%
Barotrauma (and pneumothorax) of ventilated ARDS subjects	10%
ICU Mortality	29-32%
Days of mechanical ventilation	2-8
Incidence of subjects with ARDS	
at ICU admission	10%
all ventilated subjects	24%

[4] Esteban A, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, Raymondos K, Nin N, Hurtado J, Tomicic V, González M, Elizalde J, Nightingale P, Abroug F, Pelosi P, Arabi Y, Moreno R, Jibaja M, D'Empaire G, Sandi F, Matamis D, Montañez AM, Anzueto A; VENTILA Group. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med. 2008; 177(2):170-7.

Mehta and al. [2] identified 8,309,344 cases of invasive mechanical ventilation from 1993-2009. Utilization of invasive mechanical ventilation for non-surgical indications increased from 178.9/100,000 in 1993 to 310.9/100,000 US adults in 2009. Pneumonia cases requiring invasive mechanical ventilation showed the largest increase (103.6%), whereas COPD cases remained relatively stable (2.5% increase) and HF cases decreased by 55.4%. Similar demographic and clinical changes were observed for pneumonia, COPD, and HF, with cases of invasive mechanical ventilation becoming younger, more ethnically diverse, and more frequently insured by Medicaid. Outcome trends for patients differed based on diagnosis. Adjusted hospital mortality decreased over time for cases of pneumonia (OR per 5 years=0.89, 95% CI 0.88-0.90) and COPD (OR per 5 years=0.97, 95% CI 0.97-0.98) but increased for HF (OR per 5 years=1.10, 95% CI 1.09-1.12).

Table 11: Baseline demographics and comorbidities for Invasive Mechanical Ventilation) [5]

Baseline demographics and comorbidities for 3 representative years*	1993 (n=341,164	001 (n=431,144)	2009 (n=723,310)	p-value**
Age: Mean (SD)	65.2 (17.4)	64.2 (17.7)	61.6 (17.7)	<0.0001
Male	51.4	50.9	53.2	<0.0001
Race				<0.0001
White	60.1	54.7	56.8	
Black	11.5	11.6	14.0	
Hispanic	5.5	6.4	7.9	
Other†	22.9	27.2	21.3	
Primary Payer				<0.0001
Medicare	61.5	58.4	54.4	
Medicaid	10.1	11.6	14.3	
Private Insurance	19.1	21.5	20.7	
Other†	9.4	8.5	10.6	
Comorbidities				<0.0001
No comorbidities	12.8	7.0	4.7	
1-2 comorbidities	55.1	44.2	34.6	
>2 comorbidities	32.2	48.9	60.7	
Chronic HF	27.7	27.3	22.3	<0.0001
Chronic Lung Disease	26.7	31.7	28.4	<0.0001
Valvular Heart Disease	7.1	7.8	4.0	<0.0001
Peripheral Vascular Disease	3.1	4.1	5.0	<0.0001
Hypertension	20.5	34.4	42.6	<0.0001
Paralysis	3.2	4.4	6.3	<0.0001
Other Neurologic Disorders	9.2	12.3	12.8	<0.0001
Diabetes w/o chronic complications	10.6	17.1	20.1	<0.0001
Renal Failure	4.2	8.2	15.5	<0.0001
Liver Disease	2.3	4.1	4.2	<0.0001
Metastatic Cancer	2.7	3.3	3.2	<0.0001
Obesity	1.5	3.4	7.4	<0.0001
Weight Loss	3.9	6.5	15.3	<0.0001
Alcohol Abuse	6.1	8.5	8.8	<0.0001
Drug Abuse	2.6	4.5	5.7	<0.0001

* First year (1993), middle year (2001), final year of study (2008) to convey representative temporal changes in patient characteristics.

** All statistical testes represent trends over the 17 year study sample.

† Includes individuals for whom data was missing.

Clinical manifestations and medical occurrences, unintended diseases or injuries or clinical signs that are attributed to the concurrent illness / clinical condition of critically ill subjects in an ICU include[5]:

- Death
- Barotrauma /Volutrauma (and pneumothorax) from manual or mechanical ventilation during emergency therapies etc.
- Pneumonia
- Sepsis / Infections
- ARDS
- Congestive Heart failure right and left LV
- Atrial flutter/fibrillation
- Acute myocardial infraction
- Cardiac Arrest
- Trauma / iatrogenic trauma caused by emergency therapies
- Aspiration
- Bleeding
- Gastrointestinal bleeding
- Abdominal hypertension/compartment Syndrome
- Thrombosis
- Embolism
- Allergies
- Nutrition deficiencies
- Renal failure
- Liver failure
- Critical illness neuro-myopathy
- Stroke
- Intra cerebral bleeding
- Other single- and multi-organ failure

Complications of Mechanical Ventilation include[5]:

Complications during Endotracheal intubation

- Trauma of the upper airways (especially with tracheostomy)
- Bleedings
- Gastric Aspiration

[5] Manufacturer´s State-of-the-Art Documentation, on file

Hemodynamic Effects

- High plateau pressures and PEEP can negatively impact right-ventricular preload and afterload
- Pulmonary hypertension and PEEP can result into right-to-left shunting across a patent foramen ovale and worsen hypoxemia

Oxygen Toxicity

- Reabsorption atelectasis
- Increased mortality with high FiO2

Complications of Sedation

- negative inotropy
- vasodilation
- negative and toxic cerebral effects

Effects on Respiratory Muscles and Respiratory Infections

- Disuse atrophy of the diaphragm
- Limb muscle weakness
- Diaphragm dysfunction
- Ventilation-acquired pneumonia
- Microaspiration

Ventilator-Induced Lung Injury

- Severe inflammatory response
- Barotrauma / Volutrauma

Long-term Consequences

- Impairment of physical, cognitive, and mental health
- Cognitive impairment
- Depressive symptoms

Anticipated device deficiencies from search for AE´s from clinical experience for data pertinent to INTELLiVENT-ASV [6]

The INTELLiVENT-ASV is a ventilation mode which can currently be installed on the following Hamilton Medical ventilators: HAMILTON-C1 (K181216), HAMILTON-C3 (K161450), HAMILTON-G5/S1 (K103803) and HAMILTON-C6 (510(k) submission under preparation). As this ventilation mode can only be used with the parent ventilators, the safety outcomes of INTELLiVENT-ASV may be reported as "ventilator related" in the publications. To answer this question, we contacted the corresponding authors/ senior authors of the publications (List of the publications in the Appendix-1 of Q18153), to ascertain the followings:

- If there was any INTELLiVENT-ASV, related safety issues during the study.

The responses from the corresponding authors/ senior authors were matched against the "main-statement" of the publication and presented in the Table-below.

Table 12: Responses from authors/seniors authors against the "mainstatement"

No.	Title	Design and Methods	Safety	Cumulative duration of ventilation with INTELLiVENT-ASV mode
1	Feasibility study on full closed-loop control ventilation (IntelliVent-ASV) in ICU s with acute respiratory failure: a prospective observational comparative study. Arnal, JM., Garnero, A., Novonti, D. et al. Crit Care (2013) 17: R196. https://doi.org/10.1186/cc12890	Prospective, Observational	Main statement: No safety issue occurred. Safety issues not-related to ventilation are as below: Event — No. Pneumothorax — 1 Re-intubation — 2 Deactivation of PEEP setting — 1 Deactivation of FiO2 control — 1	9408 hours
2	Safety and efficacy of a fully closed-loop control ventilation (IntelliVent-ASV®) in sedated ICU patients with acute respiratory failure: a prospective randomized crossover study	Prospective, Randomized controlled trial	Main statement: There were no safety issues requiring premature interruption of INTELLiVENT-ASV:	100 hours

6 Manufacturers Clinical Evaluation report including PMS, on file

No.	Title	Design and Methods	Safety	Cumulative duration of ventilation with INTELLiVENT-ASV mode
	Arnal, JM., Wysocki, M., Novotni, D. et al. Intensive Care Med (2012) 38: 781. https://doi.org/10.1007/s00134-012-2548-6		No events related to INTELLIVENT-ASV	
3	Closed loop ventilation mode in intensive care unit: a randomized controlled clinical trial comparing the numbers of manual ventilator setting changes. Arnal JM, Garnero A, Novotni D,et al. Minerva Anestesiol. 2018 Jan;84(1):58-67. doi: 10.23736/S0375-9393.17.11963-2.	Randomized controlled trial	Main statement: There were no safety issues requiring premature interruption of INTELLiVENT-ASV group: No events related to INTELLIVENT-ASV In the control group, the following safety events occurred: Event: No Hypercapnia: 1 Hypoxemia: 1	4320 hours
4	Evaluation of fully automated ventilation: a randomized controlled study in post-cardiac surgery patients Lellouche F, Bouchard PA, Simard S, L'Her E, Wysocki M. doi: 10.1007/s00134-012-2799-2.	Randomized controlled trial	Main statement: No safety issue occurred. Event not related to ventilation: Event: No Massive bleeding due to surgery: 1	156 hours
5	Prospective Randomized Crossover Study of a New Closed-	Randomized controlled trial	Main statement: No safety issue occurred.	334 hours

No.	Title	Design and Methods	Safety	Cumulative duration of ventilation with INTELLiVENT-ASV mode
	loop Control System Versus Pressure Support during weaning from Mechanical Ventilation Clavieras N, Wysocki M, Coisel Y, et al Anesthesiology. 2013 Sep;119(3):631-41. doi: 10.1097/ALN.0b013e3182952608.		No detailed info.	
6	Closed-loop ventilation mode (IntelliVent-ASV) in intensive care unit: a randomized trial of ventilation delivered. Bialais E, Wittebole X, Vignaux L, et al, Minerva Anestesiol. 2016 Jun;82(6):657-68.	Randomized controlled trial	Main statement: No safety issue occurred. No detailed info	5544 hours
7	Automated Weaning from Mechanical Ventilation after Off-Pump Coronary Artery Bypass Grafting Fot EV, Izotova NN, Yudina AS, et al Front Med (Lausanne). 2017 Mar 21;4:31. doi: 10.3389/fmed.2017.00031. eCollection 2017.	Randomized controlled trial	Main statement: No safety issue occurred. No events related to INTELLIVENT-ASV	58 hours
8	A prospective comparison of the efficacy and safety of fully closed-loop control ventilation (INTELLiVENT-ASV) with conventional ASV and SIMV modes	Prospective, cross over	Main statement: No safety issue occurred. The corresponding author confirmed that	40 hours

No.	Title	Design and Methods	Safety	Cumulative duration of ventilation with INTELLiVENT-ASV mode
	A Abutbul, S Sviri, V Zbedat, DM Linton, PV van Heerden Southern African Journal of Critical Care 2014;30(1):28-32. DOI:10.7196/SAJCC.197		there were no ventilator related safety issues.	
9	Fully automated closed-loop ventilation is safe and effective in post-cardiac surgery patients (Letter to the Editor) Beijers, A.J.R., Roos, A.N. & Bindels, A.J.G.H. Intensive Care Med (2014) 40: 752. https://doi.org/10.1007/s00134-014-3234-7	Prospective, Non-inferiority	Main statement: No safety issue occurred. The corresponding author confirmed that there were no ventilator related safety issues.	10,330 hours
10	Airway and trans-pulmonary driving pressures and mechanical powers selected by INTELLiVENT-ASV in passive, mechanically ventilated ICU patients. Submitted in 2019	Observational	Main statement: No safety issue occurred. The corresponding author confirmed that there were no ventilator related safety issues.	255 hours
11	A randomized controlled trial comparing full closed loop controlled ventilation (IntelliVent-ASV™) with conventional ventilation in intubated COPD subjects (interim analysis results) 38th International Symposium on Intensive care and Emergency medicine (ISICEM)	Randomized controlled trial	Main statement: No safety issue occurred. The corresponding author confirmed that there were no ventilator related safety issues. Event not related to ventilation:	2709 hours

No.	Title	Design and Methods	Safety		Cumulative duration of ventilation with INTELLiVENT-ASV mode
			Event	No	
			Hypotension(due to hypovolemia)	4	
			Re-intubation	8	

In the identified literature, there was no occurrence of adverse events, which were associated with the device in question (INTELLiVENT-ASV).

This also corresponds with the state of the art for mechanical ventilation: The subject population for which the device is intended, is a critically ill population and adverse events expected are mostly associated to the underlying disease. Their occurrence is high and ventilator-specific adverse events overlap with the expected underlying diseases and adverse events during the ICU-stay.

Anticipated device deficiencies from search for AE´s from Vigilance databases and complaints for INTELLiVENT-ASV

The INTELLIVENT-ASV ventilation mode was launched in the year 2010. Since then more than 4000 INTELLiVENT-ASV software accessories have been sold worldwide.

The table below has all INTELLIVENT-ASV sold as a software accessory worldwide.

Region	**INTELLiVENT-ASV software accessory**
Asia-Pacific	577
Europe	2190
Indian Subcontinent	24
Latin America	267
The Middle East and Africa (MEA)	518
Total	**3576**

Until now, there has been no reported problems, events, serious adverse events or recalls due to the INTELLiVENT-ASV accessory software on HAMILTON ventilators. The vigilance database searches for Bfarm (the German database and the largest European database for medical device adverse event

reporting) did not yield any events, reported problems, serious adverse events due to or related to INTELLiVENT-ASV.

Anticipated device deficiencies from risk management activities of the manufacturer:

Anticipated Serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report

- User errors such as false settings, wrong subject's conditions and offset setting
- Delayed detection of the change of the status of the subject
- Incorrect SpO2 measurement
- Incorrect CO2 measurement
- Too low signal quality
- Wrong sensor values
- Subject ventilated with the wrong target range
- PEEP too high
- Controller dysfunction
- Target shifts for SpO2 or FiO2
- Too early extubation based on only ventilatory parameters
- User thinks he is in automatic mode but is in manual mode
- controller dysfunction
- Trigger too sensitive leading to false (auto) triggering

Annex B: Summary of clinical studies using INTELLiVENT-ASV

Table 13: published studies on IV-ASV.

Study	Study Design	Compa-rator	Clinical and respiratory condition	# of subjects[1]	Time-frame	Cummulative Time (h)[1]	Outcome measure	Safety	Efficacy	Workload, user interface	Outcome
Arnal, 2012	RCT, Cross-Over	ASV	mixed subjects sedated, passive (60% ARDS)	50	2 x 2 hours	100	safety, efficacy	Need to interrupt IV-ASV[2]	Ventilatory automatic setting required to reach the targets	-	IV-ASV was safe and able set less pressure, volume and FiO2
Clavieras, 2013	RCT, Cross-Over	PS	mixed subjects spontaneous "weaning"	14	2 x 24 hours	336	efficacy, respiratory variability, safety	Time-spent in "acceptable" ventilation: RR 12-35 breaths/min, VT 5-12 ml/kg of PBW, PetCO2<55 mmHg	Oxygenation: PaO2/FiO2; ventilatory variability	Sedation scores, number of automatic and manual setting changes	IV-ASV improved PaO2/FiO2 with more setting changes
Arnal, 2013	Prospe-ctive, observa-tional	-	mixed subjects, 45 normal, 16 ARDS, 19 COPD	100	<24h intubation until extubation	9400	safety	Need to interrupt IV-ASV[3]	-	-	IV-ASV was safe. Settings were different according to the lung condition
Lellouche, 2013	RCT, Parallel Groups	CMV, then PS	postoperative (cardiac surgery under CPB)	30	Post-operative until "fast-track" extubation	100	safety, efficacy	Time-spent in "Not acceptable" range[4]	Time-spent in "Optimal" zone[3]	Number of manual ventilatory setting changes	IV-ASV maintained a predefined target range of optimal ventilation and reduced the number of interventions

Bialais, 2016	RCT, Parallel Groups	PACV, then PS	mixed subjects, 22 normal, 11 ARDS, 1 COPD, 5 brain injury	42	2 x 48 hours	2016	safety, efficacy and workload	Time-spent in "Non-optimal" zone according to clinical condition[5]	Time-spent in "Optimal" zone according to clinical condition[5]	Number of manual ventilatory setting changes and ABG	IV-ASV provided more often optimal parameters and reduced the workload
Fot, 2017	RCT, Parallel Groups	SIMV, then PS	postoperative (off-pump cardiac surgery)	18	postop until "fast-track" extubation	60	duration of MV, safety and workload	Time-spent in "Safety" zone: RR 10-30 breaths/min, VT 6-10 ml/kg of PBW, PetCO2 25-45 mmHg, SpO2>90%, Ppeak<35 cmH2O Absence of respiratory complications	Duration of postoperative ventilation	Number of manual ventilatory setting changes	IV-ASV provided a protective mechanical ventilation and reduces the workload without prolonging the duration of mechanical ventilation
Anan'ev, 2017	RCT, Cross-Over	P-CMV	TBI under controlled ventilation	12	2 x 12 hours	72	PaCO2 range, safety	Similar to [2]	PaCO2 range	Number of manual ventilatory setting changes	IV-ASV may be more effective in maintaining a PaCO2 target with fewer manual adjustment of ventilation parameters
Arnal, 2018	RCT, Parallel Groups	ACV, then PS	mixed subjects, 9 normal, 8 ARDS, 3 COPD	30	<24h intubation until extubation	3168	workload, acceptance	-	-	Manual ventilatory settings, ABG, sedation dose and user acceptance	IV-ASV reduced the number of manual and was easier to use for the caregivers

Arnal, 2019	Prospe-ctive, observa-tional		mixed subjects, 98 normal, 129 ARDS, 28 COPD	255	<48h intubation	-	Driving pressure, mechanical power (DP, MP)			IV-ASV selected safe ranges of DP et MP. In ARDS subjects, lung DP and MP were also safe
De Bie, 2020	RCT, Parallel Groups	P-CMV, then PS	postoperative (uncomplicated cardiac surgery	220	3h	330h	Time spent (and # of breaths) in "optimal" and "acceptable" safety zones.	Time spent in "critical" zone, re-intubation, postoperative pulmonary complications	Time to - spontaneous breathing, duration of mechanical ventilation	IV-ASV optimised lung protective ventilation during postoperative ventilation, with fewer episodes of severe hypoxaemia and an accelerated resumption of spontaneous breathing

Notes of Table 1:

RCT: randomized controlled trial, ASV: Adaptive Support Ventilation, PSV: Pressure Support Ventilation, CMV: Continuous Mandatory Ventilation, PACV: Pressure Assist-Control Ventilation, SIMV: Synchronized Intermittent Mandatory Ventilation, P-CMV: Pressure (controlled)-Continuous Mandatory Ventilation, ACV: Assist-Control Ventilation, CPB: cardio-pulmonary bypass, ARDS: Acute Respiratory Distress Syndrome, COPD: Chronic Obstructive Pulmonary Disease, TBI: traumatic brain injury.

1: receiving IntelliVent-ASV ventilation.

2: "Need to interrupt IV-ASV if one of the conditions below present for > 120 seconds:
SpO2 <85 % for if VT > 12 mL/kg PBW.

3: "Need to interrupt IV-ASV if one of the conditions below present for > 30 seconds:

- Pplat > 35 cmH2O,
- Vt > 10 mL/kg (12 mL/Kg for COPD),
- RR > 35 breath/min (passive subjects) or RR > 40 breath/min (active subjects).
- The oxygenation controller was deactivated if SpO2 was below 85% for more than 1 minute. Severe respiratory acidosis with pHa < 7.20.

4: "Not acceptable" or "Acceptable" (i.e., not "Optimal") if lasting more than 30 s

	Optimal	Acceptable	Not acceptable
Vt (ml/kg PBW)	6-10	>10-12	>12
PetCO2 (mmHg)	30-45	<30-25 or >45-50	<25 or ≥51
Pplat (cmH2O)	≤30	31-35	>35
SpO2 (%)	94-98 (>94 if FiO2≤40%)	93-85	<85

5: "Non optimal" or "Optimal" zones according to clinical condition

	Lung condition	**Non optimal**	**Optimal**
Vt (mL/kg IBW)	Normal lung / ARDS	<3 or >12	6-10
	Brain injury	<3 or >12	6-10
	Chronic hypercapnia	<3 or >12	7-10
RR (breath/min)	Normal lung / ARDS	<10 or >30	12-30
	Brain injury	<10 or >35	15-35
	Chronic hypercapnia	<10 or >35	15-35
Pmax (cmH2O)	Normal lung / ARDS	>30	6-25
	Brain injury	>30	6-25
	Chronic hypercapnia	>30	6-25
SpO2 (%)	Normal lung / ARDS	<90	92-96, or >96 if PEEP<8 cmH2O and FIO2<40%
	Brain injury	<90	95-99
	Chronic hypercapnia	<83	88-94, or >94 if PEEP<8 cmH2O and FIO2<40%
PetCO2 (mmHg)	Normal lung / ARDS	>55	25-45
	Brain injury	>26 or >43	30-33
	Chronic hypercapnia	<30 or >65	40-50

All studies are monocentric. Subjects recruitment consisted of adult critically ill subjects suffering from respiratory failure requiring invasive mechanical ventilation. There are 2 studies on subjects after cardiac surgery in a "fast-track" extubation procedure and 1 study on subjects suffering from traumatic brain injury with intracranial pressure monitoring, were the control of PaCO2 is a key aspect of management. In all other studies, a mixed population of adult ICU subjects was examined.

Annex C: INTELLiVENT-ASV Investigational Device Study Training Concept

Rationale:

During the study, clinicians at study centers will have to manage subjects included in the INTELLiVENT- ASV group. These subjects will be ventilated over several days. The aim of the clinician training prior to the initiation of the study is to ensure that users have a full understanding of the INTELLiVENT -ASV mode in order to use it safely and efficiently.

Participants:

Clinicians interacting with the ventilator in an ICU. Within this document clinician refers to the physician, respiratory care practitioner (RCP), and the nurse. All clinicians will be trained at a different level according to their involvement in mechanical ventilation.

Training process:

The training is divided in basic and advanced modules which consists of e-learning, frontal lectures, practical training on a simulator, and bedside training.

Basic Training:

The learning objectives are to manage sensors, to understand the ventilation controller, oxygenation controller, ASV controller and weaning tool, and to understand the alarms.

E-learning Module: Participants will be encouraged to use the e-learning modules provided by Hamilton Medical:

- ASV module
- Introduction to INTELLiVENT-ASV
- Basic operation of INTELLiVENT-ASV on G5

Frontal Lectures: A dedicated training session with frontal lectures will be provided covering the following topics, if needed:

- ASV and INTELLiVENT-ASV – Basic principles
- Weaning tool
- Sensor management
- Alarm management
- INTELLiVENT-ASV – Monitoring

Subject Simulator: A practical training using subject simulator will be provided.

Hamilton Medical developed a physiological model simulating real subject cases / scenarios that interact with the ventilator settings. The simulator (VirtuVent) is integrated directly in the Hamilton Medical G5 and S1 ventilator.

Participants will work on different scenarios:

- VirtuVent introduction
- How to set up the ventilator, sensors and initiate INTELLiVENT-ASV
- Monitoring of INTELLiVENT-ASV
- Alarm settings in INTELLiVENT-ASV
- Troubleshooting INTELLiVENT-ASV

The basic Theoretical and Practical Training program will finish with a test which has to be passed by each participant. This will be a web-based test of 20 questions with a pre-defined minimal passing score of 75%.

Advanced Theoretical and Practical Training:

The learning objectives are to be able to initiate INTELLiVENT-ASV, adjust the settings, monitor subjects and deal with the most frequent clinical situations / subject types.

E-learning Module: Participants will use the e-learning modules provided by Hamilton Medical:

- ASV module
- Introduction to INTELLiVENT-ASV
- Basic operation of INTELLiVENT-ASV on G5

Each e-learning module will finish with a test. Each participant will be required to pass this test. 75% of good answer will be required to pass the test

Frontal Lectures: A dedicated training session with frontal lectures will be provided:

- ASV and INTELLiVENT-ASV – Basic principles
- Respiratory mechanics
- ASV controller
- Ventilation controller
- Oxygenation controller
- Quick wean function
- How to use INTELLiVENT-ASV in brain injured subjects, ARDS, and COPD subjects
- Frequently asked questions and troubleshooting

Subject Simulator: A practical training using subject simulator will be provided.

Hamilton Medical developed a physiological model simulating real subject cases / scenarios that interact with the ventilator settings. The simulator (VirtuVent) is integrated directly in the Hamilton Medical G5 and S1 ventilator.

Participants will work on different scenarios:

- VirtuVent introduction
- How to set up the ventilator, sensors and initiate INTELLiVENT-ASV
- Monitoring INTELLiVENT-ASV
- Setting adjustments
- Quick wean setting and monitoring

- Alarm settings and management
- INTELLiVENT-ASV for Normal lung subject / Post cardiac surgery subject, brain injury, ARDS, and COPD subjects
- Troubleshooting INTELLiVENT-ASV

The Advanced Theoretical and Practical Training program will finish with a test which has to be passed by each participant. This will be a web-based test of several questions with a pre-defined minimal passing score of 75%.

Bedside training (in US this phase of the training will start after obtaining the IDE): As the final phase of practical training participants will manage real subjects using INTELLiVENT-ASV in order to gain bedside practice under guidance of a trained INTELLiVENT-ASV instructor. Participants will have to manage different types of subjects covering:

- Passive subject with normal lung
- Passive subject with brain injury
- Passive subject with ARDS
- COPD subject
- Spontaneously breathing subjects
- Subjects during the weaning phase

The number of subjects needed to acquire sufficient expertise will depend on the number of ICU beds, size of the clinical staff, and on the type of subjects ventilated in the ICU. This number will be adjusted to each individual study site and staff.

At sites who have had previous experience ventilating with INTELLiVENT-ASV, may have the training program partially or completely waived. This will be the case especially for sites outside of the US.

Remark: Subjects ventilated during the practical training phase will be monitored for safety events but will not be taken into consideration for the study outcome and statistics.

Annex D: List of Adverse Event

List if Adverse Event that should be recorded by the investigational sites in the EASiVENT Study.

Version 1.0 and it subsequent amendment, by reference only.

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