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T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: the multicentre randomised controlled TIP-EX protocol.

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Complete List of Authors:	<p>Thille, Arnaud; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Coudroy, Rémi; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Gacouin, Arnaud; Centre Hospitalier Universitaire de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale, Ehrmann, Stephan; Centre Hospitalier Régional Universitaire de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des pathologies respiratoires, INSERM U1100, Université de Tours</p> <p>Contou, Damien; Centre Hospitalier Victor Dupouy d'Argenteuil, Service de Réanimation Polyvalente</p> <p>Dangers, Laurence; Centre Hospitalier Universitaire Félix Guyon, Service de Réanimation Polyvalente</p> <p>Romen, Antoine; Centre Hospitalier de Pau, Service de Réanimation</p> <p>GUITTON, Christophe; Centre Hospitalier du Mans, Médecine intensive réanimation</p> <p>Lacave, Guillaume; Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale</p> <p>Quenot, Jean-Pierre; Centre Hospitalier Universitaire de Dijon, Médecine Intensive Réanimation</p> <p>Lacombe, Béatrice; Centre Hospitalier de Bretagne Sud, Réanimation polyvalente</p> <p>Pradel, Gael; Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation</p> <p>Terzi, Nicolas ; Centre Hospitalier Universitaire Grenoble Alpes, Médecine Intensive Réanimation; Université Grenoble Alpes, INSERM, U1042, HP2, Prat, Gwenaël; Centre Hospitalier Universitaire de Brest, Médecine Intensive et Réanimation</p> <p>Labro, Guylaine; Groupe Hospitalier de la Région de Mulhouse et Sud Alsace, site Emile Muller, Service de Réanimation Médicale,</p> <p>Reignier, Jean; Centre Hospitalier Universitaire de Nantes, Médecine intensive réanimation</p> <p>Beduneau, Gaetan; Centre Hospitalier Universitaire de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie Université</p>

	<p>Dellamonica, Jean ; Centre Hospitalier Universitaire de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur, Université Cote d'Azur</p> <p>Nay, Mai-Anh; Centre Hospitalier Régional d'Orleans Hôpital de La Source, Médecine Intensive Réanimation</p> <p>Rouze, Anahita; Centre Hospitalier Universitaire de Lille, Centre de Réanimation, Université de Lille</p> <p>Delbove, Agathe; Centre Hospitalier Bretagne Atlantique, Réanimation Polyvalente</p> <p>Sedillot, Nicholas; Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Réanimation Polyvalente</p> <p>Mira, Jean-Paul; Assistance Publique - Hopitaux de Paris, Groupe Hospitalier Paris Centre - Cochin University Hospital - Medical Intensive Care Unit</p> <p>Bourenne, Jeremy; Assistance Publique - Hôpitaux de Marseille, CHU La Timone 2, Médecine Intensive Réanimation, Réanimation des Urgences, Aix-Marseille Université,</p> <p>Lautrette, Alexandre; Centre Jean Perrin, Unicancer, Service de Réanimation</p> <p>Argaud, Laurent Argaud; Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive Réanimation</p> <p>Levrat, Quentin; Centre hospitalier de la Rochelle, Service de Réanimation</p> <p>Devaquet, Jérôme; Hopital Foch, Service de Réanimation Polyvalente</p> <p>Vivier, Emmanuel; Centre Hospitalier Saint Joseph Saint Luc, Reanimation Polyvalente</p> <p>Azais, Marie-Ange; Centre Hospitalier Departmental La Roche-sur-Yon, Service de Médecine Intensive et Réanimation</p> <p>Leroy, Christophe; Centre Hospitalier Emile Roux, Service de Réanimation</p> <p>DRES, Martin; Assistance Publique - Hopitaux de Paris, Hôpital Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation, Sorbonne Université</p> <p>Robert, René; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Ragot, Stéphanie; University of Poitiers, ALIVE eesearch group, CIC 1402 INSERM</p> <p>Frat, Jean-Pierre; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p>
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T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: the multicentre randomised controlled TIP-EX protocol.

Arnaud W. Thille^{1,2}, Rémi Coudroy^{1,2}, Arnaud Gacouin³, Stephan Ehrmann⁴, Damien Contou⁵, Laurence Dangers⁶, Antoine Romen⁷, Christophe Guitton⁸, Guillaume Lacave⁹, Jean-Pierre Quenot¹⁰, Béatrice La Combe¹¹, Gael Pradel¹², Nicolas Terzi¹³, Gwénaél Prat¹⁴, Guylaine Labro¹⁵, Jean Reignier¹⁶, Gaëtan Beduneau¹⁷, Jean Dellamonica¹⁸, Mai-Anh Nay¹⁹, Anahita Rouzé²⁰, Agathe Delbove²¹, Nicholas Sedillot²², Jean-Paul Mira²³, Jeremy Bourenne²⁴, Alexandre Lautrette²⁵, Laurent Argaud²⁶, Quentin Levrat²⁷, Jérôme Devaquet²⁸, Emmanuel Vivier²⁹, Marie-Ange Azais³⁰, Christophe Leroy³¹, Martin Dres³², René Robert^{1,2}, Stéphanie Ragot², Jean-Pierre Frat^{1,2}, and the REVA research network.

Affiliations :

¹CHU de Poitiers, Médecine Intensive Réanimation, Poitiers, France.

²INSERM CIC 1402 ALIVE, Université de Poitiers, Poitiers, France.

³CHU de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale, Rennes, France.

⁴CHRU de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des pathologies respiratoires, INSERM U1100, Université de Tours, Tours, France.

⁵Centre Hospitalier Victor Dupouy, Réanimation Polyvalente et Unité de Surveillance Continue, Argenteuil, France.

⁶CHU Félix Guyon, Service de Réanimation Polyvalente, Saint Denis de la Réunion, France.

⁷Centre Hospitalier de Pau, Service de Réanimation, Pau, France.

⁸Centre Hospitalier du Mans, Réanimation Médico-Chirurgicale, Le Mans, France.

⁹Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale, Le Chesnay, France.

¹⁰CHU Dijon Bourgogne, Médecine Intensive Réanimation, Dijon, France.

¹¹Centre Hospitalier Bretagne Sud, Réanimation polyvalente, Lorient, France.

¹²Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation, Aurillac, France.

¹³CHU Grenoble Alpes, Médecine Intensive Réanimation, INSERM, Université Grenoble-Alpes, U1042, HP2, Grenoble, France.

¹⁴CHU de Brest, Médecine Intensive Réanimation, Brest, France.

¹⁵Groupe Hospitalier Régional Mulhouse Sud Alsace, site Emile Muller, Service de Réanimation Médicale, Mulhouse, France.

¹⁶CHU de Nantes, Médecine Intensive Réanimation, Nantes, France.

¹⁷CHU de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie Université, Rouen, France.

1
2
3 ¹⁸CHU de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur,

4 ¹⁹Centre Hospitalier Régional d'Orléans, Médecine Intensive Réanimation, Orléans, France.

5 ²⁰CHU de Lille, Centre de Réanimation, Université de Lille, F-59000 Lille, France.

6
7
8 Université Côte d'Azur, Nice, France.

9
10 ²¹Centre Hospitalier Bretagne Atlantique, Réanimation polyvalente, Vannes, France.

11 ²²Centre Hospitalier Fleyriat, Réanimation Polyvalente, Bour en Bresse, France.

12
13 ²³Groupe Hospitalier Paris Centre, AP-HP, Hôpital Cochin, Médecine Intensive Réanimation,
14 Université de Paris, Paris, France.

15
16 ²⁴CHU La Timone 2, Médecine Intensive Réanimation, Réanimation des Urgences, Aix-Marseille
17 Université, Marseille, France.

18
19 ²⁵Centre Unicancer Jean Perrin, Réanimation, Clermont-Ferrand, France.

20 ²⁶Hôpital Edouard Herriot, Hospices Civils de Lyon, Médecine Intensive Réanimation, Lyon, France.

21
22 ²⁷Centre Hospitalier de La Rochelle, Service de Réanimation, La Rochelle, France.

23
24 ²⁸Hôpital Foch, Service de Réanimation Polyvalente, Suresnes, France.

25
26 ²⁹Hôpital Saint-Joseph Saint-Luc, Réanimation Polyvalente, Lyon, France.

27
28 ³⁰Centre Hospitalier Départemental de Vendée, Service de Médecine Intensive et Réanimation, La
29 Roche Sur Yon, France.

30
31 ³¹Centre Hospitalier Emile Roux, Service de Réanimation, Le Puy en Velay, France.

32
33 ³²Hôpital Pitié-Salpêtrière, AP-HP, Service de Pneumologie, Médecine Intensive et Réanimation,
34 Sorbonne Université, Paris, France.

35
36
37
38
39 **E-mail Authors:** aw.thille@gmail.com; r.coudroy@yahoo.fr; arnaud.gacouin@chu-rennes.fr;
40 stephanehermann@gmail.com; damien.contou@ch-argenteuil.fr; laurence.dangers@chu-reunion.fr;
41 antoine.romen@ch-pau.fr; cguitton@ch-lemans.fr; glacave@ch-versailles.fr; [pierre.quenot@chu-dijon.fr](mailto:jean-
42 <a href=); b.lacombe@ghbs.bzh; gaelpradel@hotmail.com; [grenoble.fr](mailto:nterzi@chu-
43 <a href=); gwenael.prat@chu-brest.fr; guylainelabro@hotmail.fr; jean.reignier@chu-nantes.fr;
44 gaetan.beduneau@chu-rouen.fr; dellamonica.j@chu-nice.fr; mai-anh.nay@chr-orleans.fr;
45 anahita.rouze@chru-lille.fr; agathe.delbove@ch-bretagne-atlantique.fr; nsedillot@ch-bourg01.fr;
46 jean-paul.mira@aphp.fr; jeremy.bourenne@ap-hm.fr; alexandre.lautrette@clermont.unicancer.fr;
47 laurent.argaud@chu-lyon.fr; quentin.levrat@ch-larochelle.fr; j.devaquet@hopital-foch.org;
48 evivier@ch-stjoseph-stluc-lyon.fr; marie-ange.azais@chd-vendee.fr; christophe.leroy@ch-lepuy.fr;
49 martin.dres@aphp.fr; rene.robert@chu-poitiers.fr; stephanie.ragot@univ-poitiers.fr; [pierre.frat@chu-poitiers.fr](mailto:jean-
50 <a href=);
51
52
53
54
55
56
57
58
59
60

Corresponding author : Arnaud W. Thille, Médecine Intensive Réanimation, CHU de Poitiers, 2 rue la Milétrie, 86021 Poitiers Cedex, France.

E-mail: aw.thille@gmail.com

Phone: 0033549444007

Trial registration number: NCT04227639

Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

AWT, RC, AG, SE, DC, LD, AR, CG, GL, JPQ, BLC, GP, NT, GP, GL, JR, GB, JD, MAN, AR, AD, NS, JPM, JB, AL, LA, QL, JD, EV, MAA, CL, MD, RR, SR, JPF contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Competing interests

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Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

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ABSTRACT (298)

Introduction: In ICU, the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We are hypothesizing that as compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, length of stay in ICU, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the ethics committee and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

► This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in ICUs with a high level of evidence.

► Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

► A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in ICUs.

► Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

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3 **Words count: 3985**
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6 **INTRODUCTION**

7 **Background and rationale**

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10 In ICU, the decision of extubation is a critical time because mortality is particularly high in case of
11 extubation failure leading to reintubation.¹ The overall rate of reintubation after planned extubation
12 is around 10% but may exceed 20% in patients at high-risk of extubation failure.¹ To reduce that risk,
13 guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before
14 extubation in all patients intubated at least 24h in order to mimic the post-extubation physiological
15 conditions.² A standard test for extubation readiness is a SBT with a T-piece disconnecting the patient
16 from the ventilator and providing additional oxygen (T-piece trial). Another widely used trial is
17 performed without disconnecting the patient from the ventilator, using low levels of pressure-
18 support ventilation (PSV trial). In recent large cohort studies these 2 types of SBTs were performed
19 with nearly the same frequency.^{3 4} However, these 2 trials are not equivalent in terms of patient
20 breathing effort. Physiological studies have shown that work of breathing measured during T-piece
21 was similar to work of breathing after extubation.⁵ In contrast, work of breathing is markedly lower
22 during PSV trial than during T-piece. Consequently, while PSV trial may potentially hasten extubation,
23 it may also increase the risk of reintubation by underestimating the work of breathing needed after
24 extubation.⁶

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35 A large randomised controlled trial recently found that the proportion of patients successfully
36 extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-
37 piece trial for 2 hours.⁷ In this study, reintubation rates did not differ using PSV trial or T-piece. These
38 findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten
39 extubation without an increased risk of reintubation. However, in this study the proportion of
40 patients with simple weaning was particularly high and patients with weaning difficulties were not
41 monitored up until extubation, thereby limiting the application of these findings to simple weaning.
42 Moreover, reintubation rates were particularly low meaning that the population mainly included
43 patients at low-risk of extubation failure.⁸ The latest American guidelines suggested an initial SBT
44 using PSV rather than T-piece to hasten extubation.² The strength of this recommendation was only
45 conditional given the moderate certainty of evidence. To improve the level of evidence of daily
46 clinical practice, we have decided to assess whether SBTs performed using PSV may hasten
47 extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as
48 compared to T-piece.

59 **Objectives**

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3 We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies
4 of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure.
5 Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of
6 reintubation.
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10 11 **Primary objective**

12 To compare the number of ventilator-free days within the 28 days following the initial SBT between a
13 strategy of extubation performing SBT with T-piece or with PSV.
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16 17 **Secondary objectives**

18 To compare between the 2 groups: (1) the number of ventilator-free days (including non-invasive
19 ventilation) within the 28 days following the initial SBT, (2) probability of extubation within the 72
20 hours and within the 7 days following the initial SBT, (3) proportion of patients with simple (≤ 24 h),
21 difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of patients
22 extubated after the initial SBT and not reintubated within the following 72 hours, (5) weaning
23 duration between the initial SBT and the first extubation attempt among extubated patients, (6)
24 probability of reintubation within the 72 hours and within the 7 days following extubation, (7)
25 proportion of patients with post-extubation respiratory failure within the 7 days following
26 extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.
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36 37 **Trial design**

38 The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial
39 comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will
40 randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-
41 support, with a 1:1 ratio.
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47 **METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES**

48 **Study setting**

49 The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.
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53 **Eligibility criteria**

54 **Inclusion criteria**

55 Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as
56 soon as possible once they meet all weaning criteria for an initial SBT.
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3 Patients will be considered at high-risk of reintubation according to the following criteria⁹: patients
4 older than 65 years, or those having any underlying chronic cardiac or lung disease. Underlying
5 chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined by left
6 ventricular ejection fraction $\leq 45\%$, history of cardiogenic pulmonary oedema, documented ischemic
7 heart disease or permanent atrial fibrillation. Chronic lung diseases include any underlying chronic
8 obstructive pulmonary disease, obesity-hypoventilation syndrome (OHS) or restrictive pulmonary
9 disease. The underlying lung disease will be either documented or highly suspected by the physician
10 in a patient intubated for acute hypercapnic respiratory failure.

11
12 According to the international conference consensus on weaning,¹⁰ patients will be considered as
13 ready for an initial SBT as soon as they meet all the following criteria: a respiratory rate ≤ 35 breaths
14 per minute, adequate oxygenation defined as $SpO_2 \geq 90\%$ with $FiO_2 \leq 0.4$ or $PaO_2/FiO_2 \geq 150$ mm Hg
15 with positive end-expiratory pressure (PEEP) ≤ 8 cmH₂O, hemodynamic stability with no need for
16 vasopressors (or minimal dosis), adequate cough, patient awake with a Richmond Agitation-Sedation
17 Scale between +1 and -2.¹¹

28 Exclusion criteria

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30 Patients fulfilling one of the following criteria will not be included: patients having already undergone
31 an initial SBT since intubation, patients admitted for traumatic brain injury or with pre-existing
32 peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with do-not-
33 reintubate order at time of the initial SBT, patients previously included in the study, patients without
34 health insurance coverage, people under protection (pregnant or breastfeeding women, minor
35 patients, subjects with guardianship or under law protection), or refusal to participate.

41 Intervention

42 Spontaneous breathing trials before extubation

43
44 Patients included will be randomised before the initial SBT and assigned to one of the following 2
45 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In
46 patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm
47 H₂O without PEEP.

53 Control group: T-piece trial

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55 The T-piece trial will be performed with a T-piece connected to the extremity of the endotracheal
56 tube by simply disconnecting the patient from the ventilator and providing additional oxygen (≤ 6
57 L/min). We will propose to add an oxygen flow rate of 3 L/min in patients mechanically ventilated
58 with a FiO_2 0.3 prior to the T-piece trial and 6 L/min for those mechanically ventilated with a FiO_2 0.4.
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Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H₂O) with a FiO₂ ≤ 40% without PEEP, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.¹⁰ In case of SBT success, patients will be systematically extubated the day of the trial. After a T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for at least 1-h rest before extubation to avoid exhaustion.¹²

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,¹⁰ as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO₂ persistently below 90% (or below 88% in case of underlying chronic lung disease) on FiO₂ ≥ 0.4 or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). After extubation, prophylactic use of non-invasive ventilation alternating with high-flow nasal oxygen between non-invasive ventilation sessions will be recommended in all patients for at least 48 hours according to the results of the HIGH-WEAN study.^{13 14}

Outcomes

Primary outcome

The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28.

Secondary outcomes

Secondary outcome variables include the following:

1. The number of days alive and without mechanical ventilation (including intubation and non-invasive ventilation) between the initial SBT (day 1) and day 28.
2. The number of patients extubated within the 72 hours and within the 7 days following the initial SBT.
3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7 days) or prolonged (more than 7 days) weaning.
4. The number of patients extubated after the initial SBT and not reintubated within the following 72 hours.
5. The number of days between the initial SBT and the first extubation attempt.
6. The number of patients reintubated within the 72 hours and within the 7 days following extubation.
7. The number of patients with post-extubation respiratory failure within the 7 days following extubation.
8. Length of stay in ICU.
9. Mortality in ICU, at day 28 and at day 90.

Criteria for post-extubation respiratory failure

An episode of post-extubation respiratory failure will be defined by the presence of at least two criteria among the following: a respiratory rate above 25 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as $\text{pH} < 7.35$ units and $\text{PaCO}_2 > 45$ mm Hg, hypoxemia defined as a need for FiO_2 at 50% or more to maintain SpO_2 level at least 92% or a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mm Hg.

Criteria for reintubation

To ensure the consistency of indications across sites and reduce the risk of delayed intubation patients will be immediately reintubated if at least one of the following criteria is fulfilled: severe respiratory failure, hemodynamic failure defined by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg with signs of hypoperfusion and serum lactate level greater than 2 mmol/L, neurological failure (altered consciousness with Glasgow coma scale below 12), cardiac or respiratory arrest.

Severe respiratory failure leading to reintubation will be defined by the presence of at least two criteria among the following: a respiratory rate above 35 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as $\text{pH} < 7.25$ units and $\text{PaCO}_2 > 45$ mm Hg, hypoxemia defined as a need for FiO_2 at 80% or to maintain SpO_2

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3 level at least 92% or a ratio of the partial pressure of arterial oxygen to the fraction of inspired
4 oxygen ($\text{PaO}_2/\text{FiO}_2$) < 100 mm Hg.
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8 **Sample size**

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10 We determined that enrolment of 900 patients would provide a power of 80% to show an absolute
11 prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2
12 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.
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16 **Expected number of patients to be included in the study: statistical justification**

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18 We calculated the number of patients to include based on results of our previous cohort.¹⁵ In this
19 study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for
20 reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of
21 weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.*
22 either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days.
23 According to a recent large cohort study,⁴ these patients will represent around 2 to 3% of patients.
24 Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days
25 using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would
26 provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days
27 (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV
28 trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free
29 days in this population, the number of patients needed to be included was increased by 1.045 times
30 in each group in order to compare the two groups with non-parametric tests.¹⁶ Therefore, we
31 estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and
32 secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up,
33 we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per
34 group).
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48 **Recruitment**

49 The expected initial duration of patient enrolment is 2 years, starting in January 2020.

- 51 ► End of 2018: national grant award;
- 52 ► 2019: approval by an independent ethics committee;
- 53 ► 2020-2021: inclusion of patients;
- 54 ► 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators;
- 55 ► 2021-2022: blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis
56 populations; new queries to investigators, cleaning and closure of the database;
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3 ▶ 2022-2023: data analysis, writing of the manuscript and submission for publication.
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6 **METHODS: ASSIGNMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS**

7 **Allocation and sequence intervention**

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10 After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be
11 verified by the investigator before randomization. Before the initial SBT the investigator will
12 randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will
13 be stratified on centre and carried out by connecting to the e-CRF website [14 https://chu-poitiers.hugo-online.fr/CSOnline/](https://chu-poitiers.hugo-online.fr/CSOnline/) after fulfilling the “randomisation” page including all the criteria for eligibility.
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19 **Data collection and management**

20 Data will be collected on an e-CRF by a trained investigator or research assistant at each centre.
21 Patient follow-up and data collected are detailed in the study flow chart (**Table**).
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26 **Statistical methods**

27 All the analyses will be performed by the study statistician according to a predefined statistical
28 analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of
29 less than 0.05 will be considered as indicating statistical significance.
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34 **Descriptive analysis of patient groups at baseline**

35 The analysis will be performed on an intention-to-treat basis after validation by a blind review
36 committee of the inclusion/exclusion criteria for each patient. The continuous variables will be
37 summarized with the classic parameters of descriptive analysis (median, interquartile ranges and
38 extreme values or mean and standard deviation), while indicating the number of missing data. The
39 category variables will be presented in the form of absolute frequency and percentage in each
40 modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports.
41 Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the
42 protocol will be described and analysed on a case-by-case basis.
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51 **Analysis pertaining to the main criteria of evaluation**

52 The number of ventilator-free days at day 28, defined as the number of days alive and without
53 invasive mechanic ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day
54 28, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U
55 test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical
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60 significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.^{4 15} Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

Research assistants will regularly monitor all the centres on site to check adherence to the protocol and the accuracy of the data recorded. An investigator at each centre will be responsible for daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and completing the electronic case-report form. Although the individual study assignments of the patients cannot be masked, the coordinating centre and all the investigators will remain unaware of the study group outcomes until the data will be locked.

ETHICS AND DISSEMINATION

Consent or assent

The patient will be included after having provided a written informed consent to the investigator according to the decision of the central ethics committee. If the patient is not able to understand the information given, he/she can be included if the same procedure is completed with a next of kin. After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years.

Declaration of interest

The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.

Access to data

All investigators will have access to the final data set. Investigators will make available the documents and individual data strictly required for monitoring, quality control and audit of the study to persons having access to them, in accordance with the statutory and regulatory provisions in place (articles L.1121-3 and R.5121-13 of the French Public Health Code).

Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public Involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,⁵ PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after

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3 extubation.⁶ However, no study has demonstrated an increased reintubation rate using PSV trial as
4 compared to T-trial.
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6 Recently, a large randomised controlled trial including 1153 patients found that the proportion of
7 patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30
8 minutes than using a T-piece trial for 2 hours.⁷ However, the proportion of patients with simple
9 weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%)
10 whereas usual rates in the literature are closer to 60-70%.³ Moreover, patients with difficult weaning
11 (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting
12 application of these findings to simple weaning, and not taking into account patients with weaning
13 difficulties.^{3 4} Lastly, reintubation rates were particularly low (around 11%) meaning that the
14 population mainly included patients at low-risk of extubation failure.⁸ Although an easy test using
15 PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10%
16 or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid
17 underpowering the study and so as to be able to detect the risk, we decided to focus on patients at
18 high-risk of extubation failure and to include patients with weaning difficulties. In this population at
19 high-risk of reintubation a recent post-hoc analysis from a large randomised controlled trial showed
20 that execution of an initial SBT using PSV significantly increased the proportion of patients
21 successfully extubated within the following 72 hours as compared with T-piece.¹⁷ However, a large
22 prospective clinical trial is needed to confirm these findings in this population before being in a
23 position to apply this weaning strategy to all ICU patients.
24

25 To assess as primary outcome the duration of weaning on the one the hand and the risk of
26 reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28.
27 This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of
28 reintubation) with one and the same criterion. In previous studies, primary outcome was the number
29 of patients extubated after the initial SBT and not reintubated at 48h or 72h.^{7 18 19} Although this
30 outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the
31 number of patients extubated after the initial SBT and not reintubated within the following 72h, in
32 order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may
33 influence the success of the initial SBT and duration between the initial SBT and successful
34 extubation, we will compare the proportion of patients with simple (less than 24h), difficult (between
35 24 hours and 7 days) and prolonged (more than 7 days) weaning according to type of SBT.⁴
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37 No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the
38 clinical practice of participating centers. Type of SBT may modify only the physician's decision of
39 extubation, and no other treatment will be added or modified.
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3 In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial
4 empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without
5 increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-
6 piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and
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8 therefore, this large trial may help to establish strong recommendations with a high level of evidence
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10 on a daily clinical practice for extubation in ICUs.
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Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient ¹	X			
Characteristics of the initial SBT ²	X			
Characteristics at time of extubation ³		X		
Characteristics after extubation ⁴			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(2) Characteristics of the SBT include duration of the initial SBT, vital parameters during the initial SBT, and criteria for SBT failure.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(4) Characteristics after extubation include the use and duration of non-invasive ventilation and high-flow nasal oxygen after extubation, criteria for post-extubation respiratory failure, criteria for reintubation, need for reintubation, number of days of mechanical ventilation (invasive and non-invasive), tracheostomy, and death.

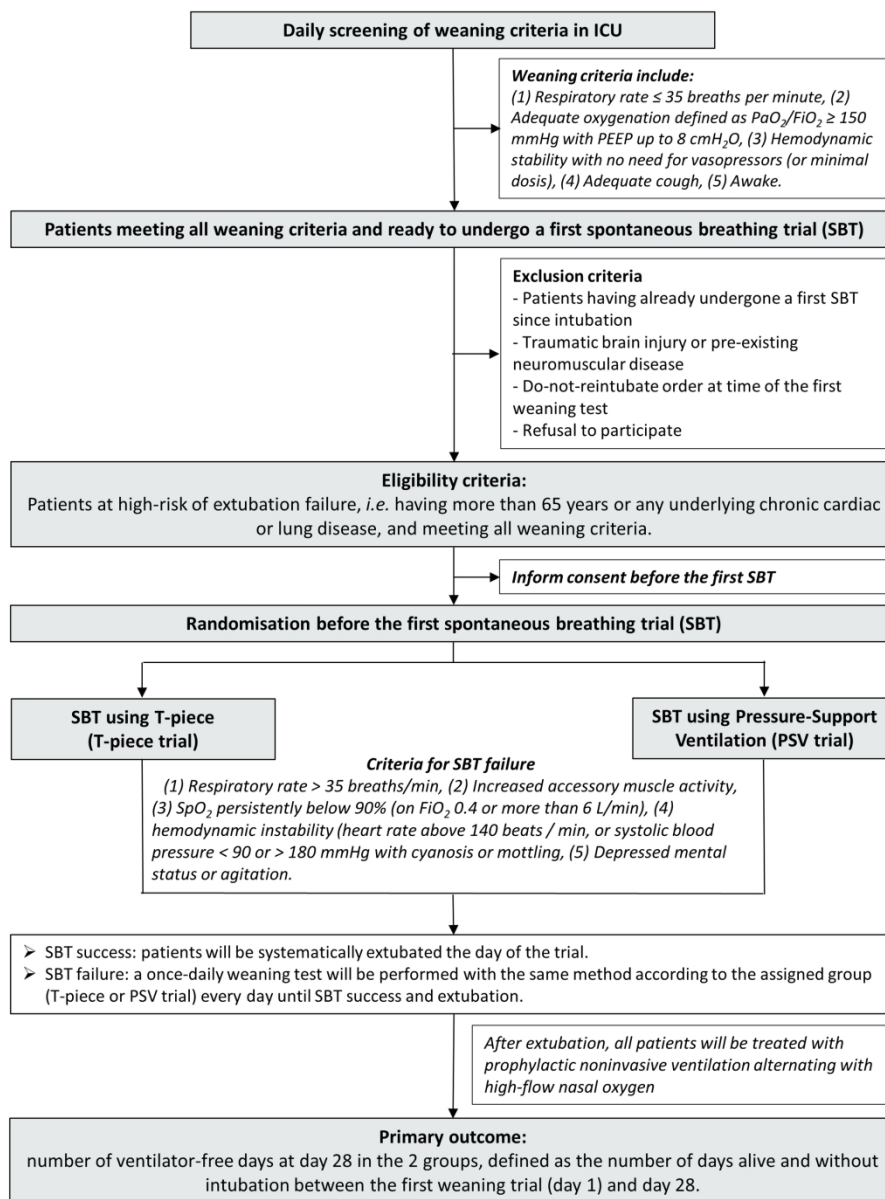


Figure 1: Flow chart of the patients and study design.

190x253mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: Page 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: Page 3	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: Page 3	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: Page 3	Sources and types of financial, material, and other support
Roles and responsibilities	5a: Page 1-3	Names, affiliations, and roles of protocol contributors
	5b: Page 3	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: Page 14	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: Page 6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: Page 6	Explanation for choice of comparators
Objectives	7: Page 6-7	Specific objectives or hypotheses

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2	Trial design	8: Page 7	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
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8	Methods: Participants, interventions, and outcomes		
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10	Study setting	9: Page 7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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14	Eligibility criteria	10: Page 7-8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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19	Interventions	11a: Page 8-9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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22		11b: Page 9	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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26		11c: Page 9	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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31		11d: Page 9	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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34	Outcomes	12: Page 9-10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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42	Participant timeline	13: Page 9-10	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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47	Sample size	14: Page 11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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51	Recruitment	15: Page 111	Strategies for achieving adequate participant enrolment to reach target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a: Page 12	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
3	generation		
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10	Allocation	16b: Page 12	
11	concealment		
12	mechanism		
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15	Implementation	16c: Page 12	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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18	Blinding	17a: Page 12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
19	(masking)		
20		17b: Page 12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a: Page 12	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
31	methods		
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39		18b: Page 12	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
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43	Data	19: Page 12	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
44	management		
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50	Statistical	20a: Page 12-13	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
51	methods		
52		20b: Page 12-13	Methods for any additional analyses (eg, subgroup and adjusted analyses)
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20c: **Page 12-13** Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a: **Page 13** Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b: **Page 13** Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22: **Page 13** Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23: **Page 13** Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24: **Page 14** Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25: **Page 14** Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a: **Page 14** Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b: **Page 14** Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27: **Page 14** How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28: **Page 14** Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29: **Page 14** Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a: Page 14	Plans for investigators and sponsor to communicate trial results
6	policy		to participants, healthcare professionals, the public, and other
7			relevant groups (eg, via publication, reporting in results
8			databases, or other data sharing arrangements), including any
9			publication restrictions
10			
11		31b	Authorship eligibility guidelines and any intended use of
12			professional writers
13			
14		31c	Plans, if any, for granting public access to the full protocol,
15			participant-level dataset, and statistical code
16			
17			
18			
19	Appendices		
20			
21	Informed consent	32	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates
23			
24	Biological	33: NA	Plans for collection, laboratory evaluation, and storage of
25	specimens		biological specimens for genetic or molecular analysis in the
26			current trial and for future use in ancillary studies, if applicable
27			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: protocol for a multicenter, randomised controlled trial (TIP-EX).

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Complete List of Authors:	<p>Thille, Arnaud; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Coudroy, Rémi; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Gacouin, Arnaud; Centre Hospitalier Universitaire de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale, Ehrmann, Stephan; Centre Hospitalier Régional Universitaire de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des pathologies respiratoires, INSERM U1100, Université de Tours</p> <p>Contou, Damien; Centre Hospitalier Victor Dupouy d'Argenteuil, Service de Réanimation Polyvalente</p> <p>Dangers, Laurence; Centre Hospitalier Universitaire Félix Guyon, Service de Réanimation Polyvalente</p> <p>Romen, Antoine; Centre Hospitalier de Pau, Service de Réanimation</p> <p>GUITTON, Christophe; Centre Hospitalier du Mans, Médecine intensive réanimation</p> <p>Lacave, Guillaume; Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale</p> <p>Quenot, Jean-Pierre; Centre Hospitalier Universitaire de Dijon, Médecine Intensive Réanimation</p> <p>Lacombe, Béatrice; Centre Hospitalier de Bretagne Sud, Réanimation polyvalente</p> <p>Pradel, Gael; Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation</p> <p>Terzi, Nicolas ; Centre Hospitalier Universitaire Grenoble Alpes, Médecine Intensive Réanimation; Université Grenoble Alpes, INSERM, U1042, HP2, Prat, Gwenaël; Centre Hospitalier Universitaire de Brest, Médecine Intensive et Réanimation</p> <p>Labro, Guylaine; Groupe Hospitalier de la Région de Mulhouse et Sud Alsace, site Emile Muller, Service de Réanimation Médicale,</p> <p>Reignier, Jean; Centre Hospitalier Universitaire de Nantes, Médecine intensive réanimation</p> <p>Beduneau, Gaetan; Centre Hospitalier Universitaire de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie Université</p>

	<p>Dellamonica, Jean ; Centre Hospitalier Universitaire de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur, Université Cote d'Azur</p> <p>Nay, Mai-Anh; Centre Hospitalier Régional d'Orleans Hôpital de La Source, Médecine Intensive Réanimation</p> <p>Rouze, Anahita; Centre Hospitalier Universitaire de Lille, Centre de Réanimation, Université de Lille</p> <p>Delbove, Agathe; Centre Hospitalier Bretagne Atlantique, Réanimation Polyvalente</p> <p>Sedillot, Nicholas; Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Réanimation Polyvalente</p> <p>Mira, Jean-Paul; Assistance Publique - Hopitaux de Paris, Groupe Hospitalier Paris Centre - Cochin University Hospital - Medical Intensive Care Unit</p> <p>Bourenne, Jeremy; Assistance Publique - Hôpitaux de Marseille, CHU La Timone 2, Médecine Intensive Réanimation, Réanimation des Urgences, Aix-Marseille Université,</p> <p>Lautrette, Alexandre; Centre Jean Perrin, Unicancer, Service de Réanimation</p> <p>Argaud, Laurent Argaud; Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive Réanimation</p> <p>Levrat, Quentin; Centre hospitalier de la Rochelle, Service de Réanimation</p> <p>Devaquet, Jérôme; Hopital Foch, Service de Réanimation Polyvalente</p> <p>Vivier, Emmanuel; Centre Hospitalier Saint Joseph Saint Luc, Reanimation Polyvalente</p> <p>Azais, Marie-Ange; Centre Hospitalier Departmental La Roche-sur-Yon, Service de Médecine Intensive et Réanimation</p> <p>Leroy, Christophe; Centre Hospitalier Emile Roux, Service de Réanimation</p> <p>DRES, Martin; Assistance Publique - Hopitaux de Paris, Hôpital Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation, Sorbonne Université</p> <p>Robert, René; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Ragot, Stéphanie; University of Poitiers, ALIVE eesearch group, CIC 1402 INSERM</p> <p>Frat, Jean-Pierre; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p>
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3 **T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in**
4 **patients at high-risk of reintubation: protocol for a multicenter, randomised controlled trial (TIP-**
5 **EX).**
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10 Arnaud W. Thille^{1,2}, Rémi Coudroy^{1,2}, Arnaud Gacouin³, Stephan Ehrmann⁴, Damien Contou⁵,
11 Laurence Dangers⁶, Antoine Romen⁷, Christophe Guitton⁸, Guillaume Lacave⁹, Jean-Pierre Quenot¹⁰,
12 Béatrice La Combe¹¹, Gael Pradel¹², Nicolas Terzi¹³, Gwénaél Prat¹⁴, Guylaine Labro¹⁵, Jean Reignier¹⁶,
13 Gaëtan Beduneau¹⁷, Jean Dellamonica¹⁸, Mai-Anh Nay¹⁹, Anahita Rouzé²⁰, Agathe Delbove²¹, Nicholas
14 Sedillot²², Jean-Paul Mira²³, Jeremy Bourenne²⁴, Alexandre Lautrette²⁵, Laurent Argaud²⁶, Quentin
15 Levrat²⁷, Jérôme Devaquet²⁸, Emmanuel Vivier²⁹, Marie-Ange Azais³⁰, Christophe Leroy³¹, Martin
16 Dres³², René Robert^{1,2}, Stéphanie Ragot², Jean-Pierre Frat^{1,2}, and the REVA research network.
17
18
19
20
21
22

23 **Affiliations :**

24
25 ¹CHU de Poitiers, Médecine Intensive Réanimation, Poitiers, France.

26 ²INSERM CIC 1402 ALIVE, Université de Poitiers, Poitiers, France.

27
28 ³CHU de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale,
29 Rennes, France.

30
31 ⁴CHRU de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des
32 pathologies respiratoires, INSERM U1100, Université de Tours, Tours, France.

33
34 ⁵Centre Hospitalier Victor Dupouy, Réanimation Polyvalente et Unité de Surveillance Continue,
35 Argenteuil, France.

36
37 ⁶CHU Félix Guyon, Service de Réanimation Polyvalente, Saint Denis de la Réunion, France.

38
39 ⁷Centre Hospitalier de Pau, Service de Réanimation, Pau, France.

40
41 ⁸Centre Hospitalier du Mans, Réanimation Médico-Chirurgicale, Le Mans, France.

42
43 ⁹Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale, Le Chesnay, France.

44
45 ¹⁰CHU Dijon Bourgogne, Médecine Intensive Réanimation, Dijon, France.

46
47 ¹¹Centre Hospitalier Bretagne Sud, Réanimation polyvalente, Lorient, France.

48
49 ¹²Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation, Aurillac, France.

50
51 ¹³CHU Grenoble Alpes, Médecine Intensive Réanimation, INSERM, Université Grenoble-Alpes, U1042,
52 HP2, Grenoble, France.

53
54 ¹⁴CHU de Brest, Médecine Intensive Réanimation, Brest, France.

55
56 ¹⁵Groupe Hospitalier Régional Mulhouse Sud Alsace, site Emile Muller, Service de Réanimation
57 Médicale, Mulhouse, France.

58
59 ¹⁶CHU de Nantes, Médecine Intensive Réanimation, Nantes, France.
60

1
2
3 ¹⁷CHU de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie
4 Université, Rouen, France.

5
6 ¹⁸CHU de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur,
7 Université Côte d'Azur, Nice, France.

8
9 ¹⁹Centre Hospitalier Régional d'Orléans, Médecine Intensive Réanimation, Orléans, France.

10
11 ²⁰CHU de Lille, Centre de Réanimation, Université de Lille, F-59000 Lille, France.

12
13 ²¹Centre Hospitalier Bretagne Atlantique, Réanimation polyvalente, Vannes, France.

14
15 ²²Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Réanimation Polyvalente, Bourg-en-Bresse,
16 France.

17
18 ²³Groupe Hospitalier Paris Centre, AP-HP, Hôpital Cochin, Médecine Intensive Réanimation,
19 Université de Paris, Paris, France.

20
21 ²⁴Assistance Publique – Hôpitaux de Marseille, CHU La Timone 2, Médecine Intensive Réanimation,
22 Réanimation des Urgences, Aix-Marseille Université, Marseille, France.

23
24 ²⁵Centre Jean Perrin, Unicancer, Service de Réanimation, Clermont-Ferrand, France.

25
26 ²⁶Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive Réanimation, Lyon, France.

27
28 ²⁷Centre Hospitalier de La Rochelle, Service de Réanimation, La Rochelle, France.

29
30 ²⁸Hôpital Foch, Service de Réanimation Polyvalente, Suresnes, France.

31
32 ²⁹Centre Hospitalier Saint-Joseph Saint-Luc, Réanimation Polyvalente, Lyon, France.

33
34 ³⁰Centre Hospitalier Départemental de Vendée, Service de Médecine Intensive et Réanimation, La
35 Roche Sur Yon, France.

36
37 ³¹Centre Hospitalier Emile Roux, Service de Réanimation, Le Puy en Velay, France.

38
39 ³²AP-HP, Hôpital Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation,
40 Sorbonne Université, Paris, France.

41
42
43
44 **E-mail Authors:** aw.thille@gmail.com; r.coudroy@yahoo.fr; arnaud.gacouin@chu-rennes.fr;
45 stephanehermann@gmail.com; damien.contou@ch-argenteuil.fr; laurence.dangers@chu-reunion.fr;
46 antoine.romen@ch-pau.fr; cguitton@ch-lemans.fr; glacave@ch-versailles.fr; [pierre.quenot@chu-dijon.fr](mailto:jean-
47 <a href=); b.lacombe@ghbs.bzh; gaelpradel@hotmail.com; [grenoble.fr](mailto:nterzi@chu-
48 <a href=); gwenael.prat@chu-brest.fr; guylainelabro@hotmail.fr; jean.reignier@chu-nantes.fr;
49 gaetan.beduneau@chu-rouen.fr; dellamonica.j@chu-nice.fr; mai-anh.nay@chr-orleans.fr;
50 anahita.rouze@chru-lille.fr; agathe.delbove@ch-bretagne-atlantique.fr; nsedillot@ch-bourg01.fr;
51 jean-paul.mira@aphp.fr; jeremy.bourenne@ap-hm.fr; alexandre.lautrette@clermont.unicancer.fr;
52 laurent.argaud@chu-lyon.fr; quentin.levrat@ch-larochelle.fr; j.devaquet@hopital-foch.org;
53 evivier@ch-stjoseph-stluc-lyon.fr; marie-ange.azais@chd-vendee.fr; christophe.leroy@ch-lepuy.fr;
54
55
56
57
58
59
60

martin.dres@aphp.fr; rene.robert@chu-poitiers.fr; stephanie.ragot@univ-poitiers.fr; jean-pierre.frat@chu-poitiers.fr;

Corresponding author : Arnaud W. Thille, Médecine Intensive Réanimation, CHU de Poitiers, 2 rue la Milétrie, 86021 Poitiers Cedex, France.

E-mail: aw.thille@gmail.com

Phone: 0033549444007

Trial registration number: NCT04227639

Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network (Réseau Européen Ventilation Artificielle) designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

AWT, RC, AG, SE, DC, LD, AR, CG, GL, JPQ, BLC, GP, NT, GP, GL, JR, GB, JD, MAN, AR, AD, NS, JPM, JB, AL, LA, QL, JD, EV, MAA, CL, MD, RR, SR, JPF contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

None

Competing interests

AWT reports financial support (payment for lectures and travel expenses coverage to attend scientific meetings) by Fisher & Paykel, Covidien, Maquet – Getinge, GE Healthcare.

J-PF reports consulting fees from Fisher & Paykel and SOS oxygène.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Data sharing

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3 Data will be made available after reasonable request has been discussed among the steering
4 committee.

5 **Provenance and peer review**

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7 Not commissioned; externally peer reviewed.
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For peer review only

ABSTRACT (300 words)

Introduction: In ICU, the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We are hypothesizing that as compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, length of stay in ICU, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the central ethics committee "Ile de France V" (2019-A02151-56) and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

► This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in ICUs with a high level of evidence.

► Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

► A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in ICUs.

► Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

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3 **Words count: 4199**
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6 **INTRODUCTION**

7 **Background and rationale**

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10 In ICU, the decision of extubation is a critical time because mortality is particularly high in case of
11 extubation failure leading to reintubation.¹ The overall rate of reintubation after planned extubation
12 is around 10% but may exceed 20% in patients at high-risk of extubation failure.¹ To reduce that risk,
13 guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before
14 extubation in all patients intubated at least 24h in order to mimic the post-extubation physiological
15 conditions.² A standard test for extubation readiness is a SBT with a T-piece disconnecting the patient
16 from the ventilator and providing additional oxygen (T-piece trial). Another widely used trial is
17 performed without disconnecting the patient from the ventilator, using low levels of pressure-
18 support ventilation (PSV trial). In recent large cohort studies these 2 types of SBTs were performed
19 with nearly the same frequency.^{3 4} However, these 2 trials are not equivalent in terms of patient
20 breathing effort. Physiological studies have shown that work of breathing measured during T-piece
21 was similar to work of breathing after extubation.⁵ In contrast, work of breathing is markedly lower
22 during PSV trial than during T-piece. Consequently, while PSV trial may potentially hasten extubation,
23 it may also increase the risk of reintubation by underestimating the work of breathing needed after
24 extubation.⁶

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35 A large randomised controlled trial recently found that the proportion of patients successfully
36 extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-
37 piece trial for 2 hours.⁷ In this study, reintubation rates did not differ using PSV trial or T-piece. These
38 findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten
39 extubation without an increased risk of reintubation. However, in this study the proportion of
40 patients with simple weaning was particularly high and patients with weaning difficulties were not
41 monitored up until extubation, thereby limiting the application of these findings to simple weaning.
42 Moreover, reintubation rates were particularly low meaning that the population mainly included
43 patients at low-risk of extubation failure.⁸ The latest American guidelines suggested an initial SBT
44 using PSV rather than T-piece to hasten extubation.² The strength of this recommendation was only
45 conditional given the moderate certainty of evidence. To improve the level of evidence of daily
46 clinical practice, we have decided to assess whether SBTs performed using PSV may hasten
47 extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as
48 compared to T-piece.

49 **Objectives**

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3 We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies
4 of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure.
5 Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of
6 reintubation.
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10 11 **Primary objective**

12 To compare the number of invasive ventilator-free days within the 28 days following the initial SBT
13 between a strategy of extubation performing SBT with T-piece or with PSV.
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17 18 **Secondary objectives**

19 To compare between the 2 groups: (1) the number of ventilator-free days (including intubation and
20 non-invasive ventilation) within the 28 days following the initial SBT, (2) probability of extubation
21 within the 72 hours and within the 7 days following the initial SBT, (3) proportion of patients with
22 simple (≤ 24 h), difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of
23 patients extubated after the initial SBT and not reintubated within the following 72 hours, (5)
24 weaning duration between the initial SBT and the first extubation attempt among extubated
25 patients, (6) probability of reintubation within the 72 hours and within the 7 days following
26 extubation, (7) proportion of patients with post-extubation respiratory failure within the 7 days
27 following extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.
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36 37 **Trial design**

38 The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial
39 comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will
40 randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-
41 support, with a 1:1 ratio.
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46 47 **METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES**

48 49 **Study setting**

50 The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.
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53 54 **Eligibility criteria**

55 56 **Inclusion criteria**

57 Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as
58 soon as possible once they meet all weaning criteria for an initial SBT.
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3 Patients will be considered at high-risk of extubation failure according to the following criteria⁹:
4 patients older than 65 years, or those having any underlying chronic cardiac or lung disease.
5 Underlying chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined
6 by left ventricular ejection fraction $\leq 45\%$, history of cardiogenic pulmonary oedema, documented
7 ischemic heart disease or permanent atrial fibrillation. Chronic lung diseases include any underlying
8 chronic obstructive pulmonary disease, obesity-hypoventilation syndrome (OHS) or restrictive
9 pulmonary disease. The underlying lung disease will be either documented or highly suspected by
10 the physician in a patient intubated for acute hypercapnic respiratory failure and having 1) a history
11 of smoking with intrinsic positive end-expiratory pressure (PEEP) during mechanical ventilation
12 and/or emphysema on chest X-ray or scanner suggesting underlying chronic obstructive pulmonary
13 disease, 2) obesity (body-mass index $> 30 \text{ kg/m}^2$) with alveolar hypoventilation ($\text{PaCO}_2 > 45 \text{ mm Hg}$)
14 suggesting obesity-hypoventilation syndrome, or 3) rib cage deformation suggesting restrictive
15 pulmonary disease.

16 According to the international conference consensus on weaning,¹⁰ patients will be considered as
17 ready for an initial SBT as soon as they meet all the following criteria: a respiratory rate ≤ 35 breaths
18 per minute, adequate oxygenation defined as $\text{SpO}_2 \geq 90\%$ with $\text{FiO}_2 \leq 0.4$ or $\text{PaO}_2/\text{FiO}_2 \geq 150 \text{ mm Hg}$
19 with positive end-expiratory pressure (PEEP) $\leq 8 \text{ cmH}_2\text{O}$, hemodynamic stability with no need for
20 vasopressors (or minimal dosis $\leq 0.3 \mu\text{g/kg/min}$), adequate cough, patient awake with a Richmond
21 Agitation-Sedation Scale between +1 and -2.¹¹

22 Exclusion criteria

23 Patients fulfilling one of the following criteria will not be included: patients having already undergone
24 an initial SBT at any time since intubation, patients admitted for traumatic brain injury or with pre-
25 existing peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with
26 do-not-reintubate order at time of the initial SBT, patients previously included in the study, patients
27 without health insurance coverage, people under protection (pregnant or breastfeeding women,
28 minor patients, subjects with guardianship or under law protection), or refusal to participate.

29 Intervention

30 Spontaneous breathing trials before extubation

31 Patients included will be randomised before the initial SBT and assigned to one of the following 2
32 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In
33 patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm
34 H_2O without PEEP.

Control group: T-piece trial

The T-piece trial will be performed with a T-piece connected to the patient connection port of the endotracheal tube and providing additional oxygen (≤ 6 L/min). We will propose to add an oxygen flow rate of 3 L/min (oxygen blend) during the T-piece trial in patients mechanically ventilated with a FiO_2 0.3 prior to the T-piece trial and 6 L/min for those mechanically ventilated with a FiO_2 0.4.

Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H_2O) with a $\text{FiO}_2 \leq 40\%$ without PEEP, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.¹⁰ In case of SBT success, patients will be systematically extubated the day of the trial. After a T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for around 1-h rest before extubation to avoid exhaustion.¹²

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,¹⁰ as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO_2 persistently below 90% (or below 88% in case of underlying chronic lung disease) on $\text{FiO}_2 \geq 0.4$ or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). After extubation, prophylactic use of non-invasive ventilation alternating with high-flow nasal oxygen between non-invasive ventilation sessions will be recommended in all patients for at least 48 hours according to the results of the HIGH-WEAN study.^{13 14}

Outcomes

Primary outcome

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3 The primary outcome is the number of ventilator-free days at day 28, defined as the number of days
4 alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial
5 SBT (day 1) and day 28.
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10 *Secondary outcomes*

11 Secondary outcome variables include the following:

- 12 1. The number of days alive and without mechanical ventilation (including intubation and non-
13 invasive ventilation) between the initial SBT (day 1) and day 28.
- 14 2. The number of patients extubated within the 72 hours and within the 7 days following the initial
15 SBT.
- 16 3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7
17 days) or prolonged (more than 7 days) weaning.
- 18 4. The number of patients extubated after the initial SBT and not reintubated within the following 72
19 hours.
- 20 5. The number of days between the initial SBT and the first extubation attempt.
- 21 6. The number of patients reintubated within the 72 hours and within the 7 days following
22 extubation.
- 23 7. The number of patients with post-extubation respiratory failure within the 7 days following
24 extubation.
- 25 8. Length of stay in ICU.
- 26 9. Mortality in ICU, at day 28 and at day 90.

27 *Criteria for post-extubation respiratory failure*

28 An episode of post-extubation respiratory failure will be defined by the presence of at least two
29 criteria among the following: a respiratory rate above 25 breaths per minute, clinical signs suggesting
30 respiratory distress with increased accessory muscle activity, respiratory acidosis defined as pH <
31 7.35 units and PaCO₂ > 45 mm Hg, hypoxemia defined as a need for FiO₂ at 50% or more to maintain
32 SpO₂ level at least 92% or a PaO₂/FiO₂ ratio < 150 mm Hg.
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40 *Criteria for reintubation*

41 To ensure the consistency of indications across sites and reduce the risk of delayed intubation
42 patients will be immediately reintubated if at least one of the following criteria is fulfilled: severe
43 respiratory failure, hemodynamic failure defined by a vasopressor requirement to maintain a mean
44 arterial pressure of 65 mm Hg with signs of hypoperfusion and serum lactate level greater than 2
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3 mmol/L, neurological failure (altered consciousness with Glasgow coma scale below 12), cardiac or
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5 respiratory arrest.

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7 Severe respiratory failure leading to reintubation will be defined by the presence of at least two
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9 criteria among the following: a respiratory rate above 35 breaths per minute, clinical signs suggesting
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11 respiratory distress with increased accessory muscle activity, respiratory acidosis defined as pH <
12
13 7.25 units and PaCO₂ > 45 mm Hg, hypoxemia defined as a need for FiO₂ at 80% or to maintain SpO₂
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15 level at least 92% or a ratio of the partial pressure of arterial oxygen to the fraction of inspired
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17 oxygen (PaO₂/FiO₂) < 100 mm Hg.

18 **Sample size**

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20 We determined that enrolment of 900 patients would provide a power of 80% to show an absolute
21
22 prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2
23
24 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.

25 **Expected number of patients to be included in the study: statistical justification**

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27 We calculated the number of patients to include based on results of our previous cohort.¹⁵ In this
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29 study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for
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31 reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of
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33 weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.*
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35 either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days.
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37 According to a recent large cohort study,⁴ these patients will represent around 2 to 3% of patients.
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39 Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days
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41 using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would
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43 provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days
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45 (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV
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47 trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free
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49 days in this population, the number of patients needed to be included was increased by 1.045 times
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51 in each group in order to compare the two groups with non-parametric tests.¹⁶ Therefore, we
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53 estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and
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55 secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up,
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57 we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per
58
59 group).

60 **Recruitment**

The expected initial duration of patient enrolment is 2 years, starting in January 2020.

- ▶ End of 2018: national grant award;
- ▶ 2019: approval by an independent ethics committee;
- ▶ 2020-2021: inclusion of patients (the first participant was enrolled the 31st January 2020)
- ▶ 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;
- ▶ 2022-2023: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be verified by the investigator before randomization. Before the initial SBT the investigator will randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will be stratified on centre and carried out by connecting to the electronic case report form (e-CRF) website <https://chu-poitiers.hugo-online.fr/CSOnline/> after fulfilling the “randomisation” page including all the criteria for eligibility.

Data collection and management

Data will be collected on an e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart (**Table 1**).

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion/exclusion criteria for each patient. The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described and analysed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

The number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.^{4 15} Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

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3 Research assistants from the coordinating centre will regularly monitor all the centres on site to
4 check adherence to the protocol and the accuracy of the recorded data. After being trained to
5 conduct the protocol and to fulfil the e-CRF, an investigator at each centre will be responsible for
6 daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and
7 completing the electronic case-report form. Although the individual study assignments of the
8 patients cannot be masked, the coordinating centre and all the investigators will remain unaware of
9 the study group outcomes until the database will be locked.
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16 **ETHICS AND DISSEMINATION**

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18 The study has been approved by the central ethics committee (Ethics Committee Ile de France V,
19 Paris, France) with the registration number 2019-A02151-56 (07 October 2019).
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23 **Consent or assent**

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25 The patient will be included after having provided a written informed consent to the investigator
26 according to the decision of the central ethics committee. If the patient is not able to understand the
27 information given, he/she can be included if the same procedure is completed with a next of kin.
28 After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.
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33 **Confidentiality**

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35 Data will be handled according to French law. Coding subjects will be done by recording the first
36 letter of the name and forename, accompanied by a single study identifier indicating the order of
37 subject inclusion, in order to store anonymized data in the e-CRF. The sponsor will ensure that each
38 study participant has given his/her consent for access to his/her personal data that is strictly required
39 for quality control of the study. All original records will be archived at trial sites for 15 years
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43 **Declaration of interest**

44
45 The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with
46 funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de
47 Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.
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51 **Access to data**

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53 All investigators will have access to the final data set. Investigators will make available the
54 documents and individual data strictly required for monitoring, quality control and audit of the study
55 to persons having access to them, in accordance with the statutory and regulatory provisions in place
56 (articles L.1121-3 and R.5121-13 of the French Public Health Code).
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Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,⁵ PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after extubation.⁶ However, no study has demonstrated an increased reintubation rate using PSV trial as compared to T-trial.

Recently, a large randomised controlled trial including 1153 patients found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.⁷ However, the proportion of patients with simple weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%) whereas usual rates in the literature are closer to 60-70%.³ Moreover, patients with difficult weaning (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting application of these findings to simple weaning, and not taking into account patients with weaning difficulties.^{3 4} Lastly, reintubation rates were particularly low (around 11%) meaning that the population mainly included patients at low-risk of extubation failure.⁸ Although an easy test using PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10% or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid underpowering the study and so as to be able to detect the risk, we decided to focus on patients at high-risk of extubation failure and to include patients with weaning difficulties. In this population at high-risk of reintubation a recent post-host analysis from a large randomised controlled trial showed that execution of an initial SBT using PSV significantly increased the proportion of patients successfully extubated within the following 72 hours as compared with T-piece.¹⁷ However, a large prospective clinical trial is needed to confirm these findings in this population before being in a position to apply this weaning strategy to all ICU patients.

To assess as primary outcome the duration of weaning on the one the hand and the risk of reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28.

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2
3 This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of
4 reintubation) with one and the same criterion. In previous studies, primary outcome was the number
5 of patients extubated after the initial SBT and not reintubated at 48h or 72h.^{7 18 19} Although this
6 outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the
7 number of patients extubated after the initial SBT and not reintubated within the following 72h, in
8 order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may
9 influence the success of the initial SBT and duration between the initial SBT and successful
10 extubation, we will compare the proportion of patients with simple, difficult and prolonged weaning
11 according to type of SBT. Simple weaning includes patients extubated within the first 24 hours after
12 the initial SBT, difficult weaning includes patients extubated between 24 hours and 7 days after the
13 initial SBT, and prolonged weaning includes patients extubated more than 7 days after the initial
14 SBT.⁴

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16 No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the
17 clinical practice of participating centers. Type of SBT may modify only the physician's decision of
18 extubation, and no other treatment will be added or modified.

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20 In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial
21 empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without
22 increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-
23 piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and
24 therefore, this large trial may help to establish strong recommendations with a high level of evidence
25 on a daily clinical practice for extubation in ICUs.

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For peer review only

Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient ¹	X			
Characteristics of the initial SBT ²	X			
Characteristics at time of extubation ³		X		
Characteristics after extubation ⁴			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(2) Characteristics of the SBT include duration, type and settings of the initial SBT, vital parameters at the end of the initial SBT, and criteria for SBT failure.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(4) Characteristics after extubation include the use and duration of non-invasive ventilation and high-flow nasal oxygen after extubation (as well prophylactic use as rescue therapy to treat post-extubation respiratory failure), criteria for post-extubation respiratory failure, criteria for reintubation, need for reintubation, number of days of mechanical ventilation (invasive and non-invasive), tracheostomy, and death.

FIGURE LEGEND

Figure 1: Flow chart of the patients and study design.

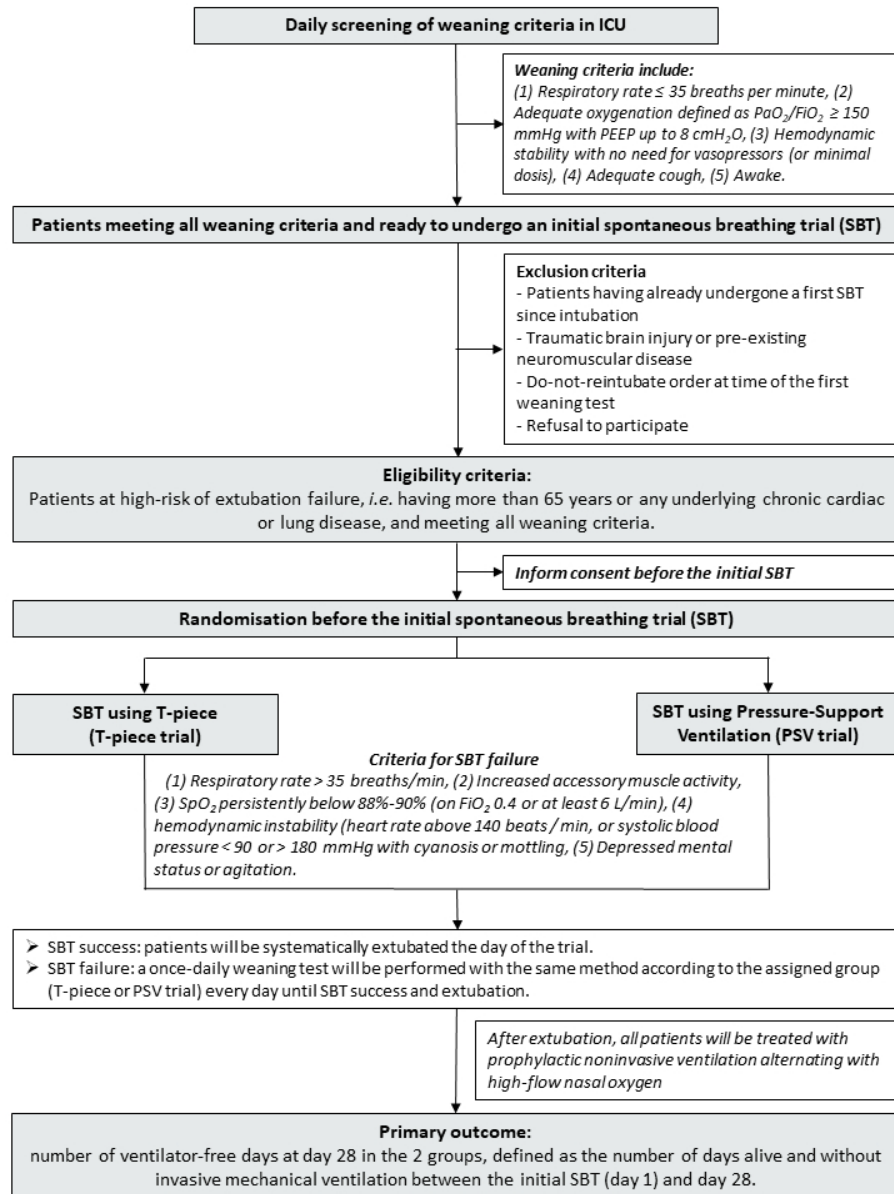


Figure 1: Flow chart of the patients and study design.

190x254mm (96 x 96 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: Page 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: Page 3	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: Page 3	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: Page 3	Sources and types of financial, material, and other support
Roles and responsibilities	5a: Page 1-3	Names, affiliations, and roles of protocol contributors
	5b: Page 3	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: Page 14	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: Page 6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: Page 6	Explanation for choice of comparators
Objectives	7: Page 6-7	Specific objectives or hypotheses

1			
2	Trial design	8: Page 7	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
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8	Methods: Participants, interventions, and outcomes		
9			
10	Study setting	9: Page 7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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13			
14	Eligibility criteria	10: Page 7-8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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19	Interventions	11a: Page 8-9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
20			
21			
22		11b: Page 9	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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26		11c: Page 9	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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30			
31		11d: Page 9	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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33			
34	Outcomes	12: Page 9-10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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42	Participant timeline	13: Page 9-10	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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47	Sample size	14: Page 11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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51	Recruitment	15: Page 111	Strategies for achieving adequate participant enrolment to reach target sample size
52			
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Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	16a: Page 12	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
3	generation		
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10	Allocation	16b: Page 12	
11	concealment		
12	mechanism		
13			
14			
15	Implementation	16c: Page 12	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
16			
17			
18	Blinding	17a: Page 12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
19	(masking)		
20		17b: Page 12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a: Page 12	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
31	methods		
32			
33		18b: Page 12	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
34			
35		19: Page 12	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
36	Data		
37	management		
38			
39			
40		20a: Page 12-13	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
41	Statistical		
42	methods	20b: Page 12-13	Methods for any additional analyses (eg, subgroup and adjusted analyses)
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20c: **Page 12-13** Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a: **Page 13** Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b: **Page 13** Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22: **Page 13** Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23: **Page 13** Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24: **Page 14** Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25: **Page 14** Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a: **Page 14** Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b: **Page 14** Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27: **Page 14** How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28: **Page 14** Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29: **Page 14** Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a: Page 14	Plans for investigators and sponsor to communicate trial results
6	policy		to participants, healthcare professionals, the public, and other
7			relevant groups (eg, via publication, reporting in results
8			databases, or other data sharing arrangements), including any
9			publication restrictions
10			
11		31b	Authorship eligibility guidelines and any intended use of
12			professional writers
13			
14		31c	Plans, if any, for granting public access to the full protocol,
15			participant-level dataset, and statistical code
16			
17			
18			
19	Appendices		
20			
21	Informed consent	32: model	Model consent form and other related documentation given to
22	materials	consent form	participants and authorised surrogates
23		available in	
24		supplementary	
25		files	
26			
27	Biological	33: NA	Plans for collection, laboratory evaluation, and storage of
28	specimens		biological specimens for genetic or molecular analysis in the
29			current trial and for future use in ancillary studies, if applicable
30			

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32 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013

33 Explanation & Elaboration for important clarification on the items. Amendments to the

34 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

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BMJ Open

T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in patients at high-risk of reintubation: protocol for a multicenter, randomised controlled trial (TIP-EX).

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Complete List of Authors:	<p>Thille, Arnaud; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Coudroy, Rémi; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Gacouin, Arnaud; Centre Hospitalier Universitaire de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale, Ehrmann, Stephan; Centre Hospitalier Régional Universitaire de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des pathologies respiratoires, INSERM U1100, Université de Tours</p> <p>Contou, Damien; Centre Hospitalier Victor Dupouy d'Argenteuil, Service de Réanimation Polyvalente</p> <p>Dangers, Laurence; Centre Hospitalier Universitaire Félix Guyon, Service de Réanimation Polyvalente</p> <p>Romen, Antoine; Centre Hospitalier de Pau, Service de Réanimation</p> <p>GUITTON, Christophe; Centre Hospitalier du Mans, Médecine intensive réanimation</p> <p>Lacave, Guillaume; Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale</p> <p>Quenot, Jean-Pierre; Centre Hospitalier Universitaire de Dijon, Médecine Intensive Réanimation</p> <p>Lacombe, Béatrice; Centre Hospitalier de Bretagne Sud, Réanimation polyvalente</p> <p>Pradel, Gael; Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation</p> <p>Terzi, Nicolas ; Centre Hospitalier Universitaire Grenoble Alpes, Médecine Intensive Réanimation; Université Grenoble Alpes, INSERM, U1042, HP2, Prat, Gwenaël; Centre Hospitalier Universitaire de Brest, Médecine Intensive et Réanimation</p> <p>Labro, Guylaine; Groupe Hospitalier de la Région de Mulhouse et Sud Alsace, site Emile Muller, Service de Réanimation Médicale,</p> <p>Reignier, Jean; Centre Hospitalier Universitaire de Nantes, Médecine intensive réanimation</p> <p>Beduneau, Gaetan; Centre Hospitalier Universitaire de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie Université</p>

	<p>Dellamonica, Jean ; Centre Hospitalier Universitaire de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur, Université Cote d'Azur</p> <p>Nay, Mai-Anh; Centre Hospitalier Régional d'Orleans Hôpital de La Source, Médecine Intensive Réanimation</p> <p>Rouze, Anahita; Centre Hospitalier Universitaire de Lille, Centre de Réanimation, Université de Lille</p> <p>Delbove, Agathe; Centre Hospitalier Bretagne Atlantique, Réanimation Polyvalente</p> <p>Sedillot, Nicholas; Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Réanimation Polyvalente</p> <p>Mira, Jean-Paul; Assistance Publique - Hopitaux de Paris, Groupe Hospitalier Paris Centre - Cochin University Hospital - Medical Intensive Care Unit</p> <p>Bourenne, Jeremy; Assistance Publique - Hôpitaux de Marseille, CHU La Timone 2, Médecine Intensive Réanimation, Réanimation des Urgences, Aix-Marseille Université,</p> <p>Lautrette, Alexandre; Centre Jean Perrin, Unicancer, Service de Réanimation</p> <p>Argaud, Laurent Argaud; Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive Réanimation</p> <p>Levrat, Quentin; Centre hospitalier de la Rochelle, Service de Réanimation</p> <p>Devaquet, Jérôme; Hopital Foch, Service de Réanimation Polyvalente</p> <p>Vivier, Emmanuel; Centre Hospitalier Saint Joseph Saint Luc, Reanimation Polyvalente</p> <p>Azais, Marie-Ange; Centre Hospitalier Departmental La Roche-sur-Yon, Service de Médecine Intensive et Réanimation</p> <p>Leroy, Christophe; Centre Hospitalier Emile Roux, Service de Réanimation</p> <p>DRES, Martin; Assistance Publique - Hopitaux de Paris, Hôpital Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation, Sorbonne Université</p> <p>Robert, René; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p> <p>Ragot, Stéphanie; University of Poitiers, ALIVE eesearch group, CIC 1402 INSERM</p> <p>Frat, Jean-Pierre; Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation; University of Poitiers, ALIVE research group, CIC 1402 INSERM</p>
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3 **T-piece versus pressure-support ventilation for spontaneous breathing trials before extubation in**
4 **patients at high-risk of reintubation: protocol for a multicenter, randomised controlled trial (TIP-**
5 **EX).**
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10 Arnaud W. Thille^{1,2}, Rémi Coudroy^{1,2}, Arnaud Gacouin³, Stephan Ehrmann⁴, Damien Contou⁵,
11 Laurence Dangers⁶, Antoine Romen⁷, Christophe Guitton⁸, Guillaume Lacave⁹, Jean-Pierre Quenot¹⁰,
12 Béatrice La Combe¹¹, Gael Pradel¹², Nicolas Terzi¹³, Gwénaél Prat¹⁴, Guylaine Labro¹⁵, Jean Reignier¹⁶,
13 Gaëtan Beduneau¹⁷, Jean Dellamonica¹⁸, Mai-Anh Nay¹⁹, Anahita Rouzé²⁰, Agathe Delbove²¹, Nicholas
14 Sedillot²², Jean-Paul Mira²³, Jeremy Bourenne²⁴, Alexandre Lautrette²⁵, Laurent Argaud²⁶, Quentin
15 Levrat²⁷, Jérôme Devaquet²⁸, Emmanuel Vivier²⁹, Marie-Ange Azais³⁰, Christophe Leroy³¹, Martin
16 Dres³², René Robert^{1,2}, Stéphanie Ragot², Jean-Pierre Frat^{1,2}, and the REVA research network.
17
18
19
20
21
22

23 **Affiliations :**

24
25 ¹CHU de Poitiers, Médecine Intensive Réanimation, Poitiers, France.

26 ²INSERM CIC 1402 ALIVE, Université de Poitiers, Poitiers, France.

27
28 ³CHU de Rennes, Hôpital Ponchaillou, Service des Maladies Infectieuses et Réanimation Médicale,
29 Rennes, France.

30
31 ⁴CHRU de Tours, Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des
32 pathologies respiratoires, INSERM U1100, Université de Tours, Tours, France.

33
34 ⁵Centre Hospitalier Victor Dupouy, Réanimation Polyvalente et Unité de Surveillance Continue,
35 Argenteuil, France.

36
37 ⁶CHU Félix Guyon, Service de Réanimation Polyvalente, Saint Denis de la Réunion, France.

38
39 ⁷Centre Hospitalier de Pau, Service de Réanimation, Pau, France.

40
41 ⁸Centre Hospitalier du Mans, Réanimation Médico-Chirurgicale, Le Mans, France.

42
43 ⁹Centre Hospitalier de Versailles, Service de Réanimation Médico-Chirurgicale, Le Chesnay, France.

44
45 ¹⁰CHU Dijon Bourgogne, Médecine Intensive Réanimation, Dijon, France.

46
47 ¹¹Centre Hospitalier Bretagne Sud, Réanimation polyvalente, Lorient, France.

48
49 ¹²Centre Hospitalier Henri Mondor d'Aurillac, Service de Réanimation, Aurillac, France.

50
51 ¹³CHU Grenoble Alpes, Médecine Intensive Réanimation, INSERM, Université Grenoble-Alpes, U1042,
52 HP2, Grenoble, France.

53
54 ¹⁴CHU de Brest, Médecine Intensive Réanimation, Brest, France.

55
56 ¹⁵Groupe Hospitalier Régional Mulhouse Sud Alsace, site Emile Muller, Service de Réanimation
57 Médicale, Mulhouse, France.

58
59 ¹⁶CHU de Nantes, Médecine Intensive Réanimation, Nantes, France.
60

1
2
3 ¹⁷CHU de Rouen, Hôpital Charles Nicolle, Département de Réanimation Médicale, Normandie
4 Université, Rouen, France.

5
6 ¹⁸CHU de Nice, Réanimation Médicale Archet 1, UR2CA-Unité de Recherche Clinique Côte d'Azur,
7 Université Côte d'Azur, Nice, France.

8
9 ¹⁹Centre Hospitalier Régional d'Orléans, Médecine Intensive Réanimation, Orléans, France.

10
11 ²⁰CHU de Lille, Centre de Réanimation, Université de Lille, F-59000 Lille, France.

12
13 ²¹Centre Hospitalier Bretagne Atlantique, Réanimation polyvalente, Vannes, France.

14
15 ²²Centre Hospitalier de Bourg-en-Bresse, Hôpital Fleyriat, Réanimation Polyvalente, Bourg-en-Bresse,
16 France.

17
18 ²³Groupe Hospitalier Paris Centre, AP-HP, Hôpital Cochin, Médecine Intensive Réanimation,
19 Université de Paris, Paris, France.

20
21 ²⁴Assistance Publique – Hôpitaux de Marseille, CHU La Timone 2, Médecine Intensive Réanimation,
22 Réanimation des Urgences, Aix-Marseille Université, Marseille, France.

23
24 ²⁵Centre Jean Perrin, Unicancer, Service de Réanimation, Clermont-Ferrand, France.

25
26 ²⁶Hospices Civils de Lyon, Hôpital Edouard Herriot, Médecine Intensive Réanimation, Lyon, France.

27
28 ²⁷Centre Hospitalier de La Rochelle, Service de Réanimation, La Rochelle, France.

29
30 ²⁸Hôpital Foch, Service de Réanimation Polyvalente, Suresnes, France.

31
32 ²⁹Centre Hospitalier Saint-Joseph Saint-Luc, Réanimation Polyvalente, Lyon, France.

33
34 ³⁰Centre Hospitalier Départemental de Vendée, Service de Médecine Intensive et Réanimation, La
35 Roche Sur Yon, France.

36
37 ³¹Centre Hospitalier Emile Roux, Service de Réanimation, Le Puy en Velay, France.

38
39 ³²AP-HP, Hôpital Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation,
40 Sorbonne Université, Paris, France.

41
42
43
44 **E-mail Authors:** aw.thille@gmail.com; r.coudroy@yahoo.fr; arnaud.gacouin@chu-rennes.fr;
45 stephanehermann@gmail.com; damien.contou@ch-argenteuil.fr; laurence.dangers@chu-reunion.fr;
46 antoine.romen@ch-pau.fr; cguitton@ch-lemans.fr; glacave@ch-versailles.fr; [pierre.quenot@chu-dijon.fr](mailto:jean-
47 <a href=); b.lacombe@ghbs.bzh; gaelpradel@hotmail.com; [grenoble.fr](mailto:nterzi@chu-
48 <a href=); gwenael.prat@chu-brest.fr; guylainelabro@hotmail.fr; jean.reignier@chu-nantes.fr;
49 gaetan.beduneau@chu-rouen.fr; dellamonica.j@chu-nice.fr; mai-anh.nay@chr-orleans.fr;
50 anahita.rouze@chru-lille.fr; agathe.delbove@ch-bretagne-atlantique.fr; nsedillot@ch-bourg01.fr;
51 jean-paul.mira@aphp.fr; jeremy.bourenne@ap-hm.fr; alexandre.lautrette@clermont.unicancer.fr;
52 laurent.argaud@chu-lyon.fr; quentin.levrat@ch-larochelle.fr; j.devaquet@hopital-foch.org;
53 evivier@ch-stjoseph-stluc-lyon.fr; marie-ange.azais@chd-vendee.fr; christophe.leroy@ch-lepuy.fr;
54
55
56
57
58
59
60

martin.dres@aphp.fr; rene.robert@chu-poitiers.fr; stephanie.ragot@univ-poitiers.fr; jean-pierre.frat@chu-poitiers.fr;

Corresponding author : Arnaud W. Thille, Médecine Intensive Réanimation, CHU de Poitiers, 2 rue la Milétrie, 86021 Poitiers Cedex, France.

E-mail: aw.thille@gmail.com

Phone: 0033549444007

Trial registration number: NCT04227639

Contributors

AWT, RC and J-PF, in collaboration with all authors and the REVA network (Réseau Européen Ventilation Artificielle) designed the study and wrote the manuscript together. SR provided substantial contributions to the conception and design of the study, and wrote the statistical analysis plan and estimated the sample size with AWT.

AWT, RC, AG, SE, DC, LD, AR, CG, GL, JPQ, BLC, GP, NT, GP, GL, JR, GB, JD, MAN, AR, AD, NS, JPM, JB, AL, LA, QL, JD, EV, MAA, CL, MD, RR, SR, JPF contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors give their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

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Disclaimer

None

Competing interests

AWT reports financial support (payment for lectures and travel expenses coverage to attend scientific meetings) by Fisher & Paykel, Covidien, Maquet – Getinge, GE Healthcare.

J-PF reports consulting fees from Fisher & Paykel and SOS oxygène.

Ethics approval

The study has been approved by the central ethics committee (Ethics Committee Ile de France V, Paris, France) with the registration number 2019-A02151-56 (07 October 2019).

Data sharing

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3 Data will be made available after reasonable request and it has been discussed among the steering
4 committee.
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6 **Provenance and peer review**

7 Not commissioned; externally peer reviewed.
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For peer review only

ABSTRACT (300 words)

Introduction: In intensive care unit (ICU), the decision of extubation is a critical time because mortality is particularly high in case of reintubation. To reduce that risk, guidelines recommend to systematically perform a spontaneous breathing trial (SBT) before extubation in order to mimic the post-extubation physiological conditions. SBT is usually performed with a T-piece disconnecting the patient from the ventilator or with low levels of pressure-support ventilation (PSV). However, work of breathing is lower during PSV than during T-piece. Consequently, while PSV trial may hasten extubation, it may also increase the risk of reintubation. We hypothesize that, compared to T-piece, SBT performed using PSV may hasten extubation without increasing the risk of reintubation.

Methods and analysis: This study is an investigator-initiated, multicentre randomised controlled trial comparing T-piece versus PSV for SBTs in patients at high-risk of reintubation in ICUs. Nine-hundred patients will be randomised with a 1:1 ratio in two groups according to the type of SBT. The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation between the initial SBT (day 1) and day 28. Secondary outcomes include the number of days between the initial SBT and the first extubation attempt, weaning difficulty, the number of patients extubated after the initial SBT and not reintubated within the following 72 hours, the number of patients extubated within the 7 days following the initial SBT, the number of patients reintubated within the 7 days following extubation, in-ICU length of stay, and mortality in ICU, at day 28 and at day 90.

Ethics and dissemination: The study has been approved by the central ethics committee "Ile de France V" (2019-A02151-56) and patients will be included after informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number: NCT04227639

Strengths and limitations of the study

► This large randomised controlled trial may help to establish strong recommendations on daily clinical practice for extubation in intensive care units with a high level of evidence.

► Spontaneous breathing trials performed using T-piece or pressure-support ventilation have never been compared in the subset of patients at high-risk of reintubation.

► A large population of patients considered to be at high-risk for reintubation will be included. Patients older than 65 years or those with an underlying chronic cardiac or lung disease are easy to identify in clinical practice and represent nearly half of the patients extubated in intensive care units.

► Limitation: The individual study assignments of the patients will not be masked. Given the characteristics of the two strategies under evaluation, a double-blind trial is not possible.

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3 **Words count: 4236**
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6 **INTRODUCTION**

7 **Background and rationale**

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10 In intensive care unit (ICU), the decision of extubation is a critical time because mortality is
11 particularly high in case of extubation failure leading to reintubation.¹ The overall rate of
12 reintubation after planned extubation is around 10% but may exceed 20% in patients at high-risk of
13 extubation failure.¹ To reduce that risk, guidelines recommend to systematically perform a
14 spontaneous breathing trial (SBT) before extubation in all patients intubated at least 24h in order to
15 mimic the post-extubation physiological conditions.² A standard test for extubation readiness is a SBT
16 with a T-piece disconnecting the patient from the ventilator and providing additional oxygen (T-piece
17 trial). Another widely used trial is performed without disconnecting the patient from the ventilator,
18 using low levels of pressure-support ventilation (PSV trial). In recent large cohort studies these 2
19 types of SBTs were performed with nearly the same frequency.^{3 4} However, these 2 trials are not
20 equivalent in terms of patient breathing effort. Physiological studies have shown that work of
21 breathing measured during T-piece was similar to work of breathing after extubation.⁵ In contrast,
22 work of breathing is markedly lower during PSV trial than during T-piece. Consequently, while PSV
23 trial may potentially hasten extubation, it may also increase the risk of reintubation by
24 underestimating the work of breathing needed after extubation.⁶

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35 A large randomised controlled trial recently found that the proportion of patients successfully
36 extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-
37 piece trial for 2 hours.⁷ In this study, reintubation rates did not differ using PSV trial or T-piece. These
38 findings confirm that PSV trial is an easier test to pass than T-piece trial, and that it may hasten
39 extubation without an increased risk of reintubation. However, in this study the proportion of
40 patients with simple weaning was particularly high and patients with weaning difficulties were not
41 monitored up until extubation, thereby limiting the application of these findings to simple weaning.
42 Moreover, reintubation rates were particularly low meaning that the population mainly included
43 patients at low-risk of extubation failure.⁸ The latest American guidelines suggested an initial SBT
44 using PSV rather than T-piece to hasten extubation.² The strength of this recommendation was only
45 conditional given the moderate certainty of evidence. To improve the level of evidence of daily
46 clinical practice, we have decided to assess whether SBTs performed using PSV may hasten
47 extubation without increasing the risk of reintubation in patients at high-risk of extubation failure as
48 compared to T-piece.
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Objectives

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3 We aim to conduct a prospective multicentre randomised controlled trial comparing two strategies
4 of extubation performing SBT with T-piece or with PSV in patients at high-risk of extubation failure.
5 Our hypothesis is that SBTs with PSV may hasten extubation without increasing the risk of
6 reintubation.
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10 11 **Primary objective**

12 To compare the number of invasive ventilator-free days within the 28 days following the initial SBT
13 between a strategy of extubation performing SBT with T-piece or with PSV.
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17 18 **Secondary objectives**

19 To compare between the 2 groups: (1) the number of ventilator-free days (including intubation and
20 non-invasive ventilation) within the 28 days following the initial SBT, (2) probability of extubation
21 within the 72 hours and within the 7 days following the initial SBT, (3) proportion of patients with
22 simple (≤ 24 h), difficult (> 24 hours and ≤ 7 days) or prolonged (> 7 days) weaning, (4) proportion of
23 patients extubated after the initial SBT and not reintubated within the following 72 hours, (5)
24 weaning duration between the initial SBT and the first extubation attempt among extubated
25 patients, (6) probability of reintubation within the 72 hours and within the 7 days following
26 extubation, (7) proportion of patients with post-extubation respiratory failure within the 7 days
27 following extubation, (8) length of stay in ICU, (9) the mortality in ICU, at day 28 and at day 90.
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36 37 **Trial design**

38 The TIP-EX study is an investigator-initiated, multicentre, randomised, controlled, open-label trial
39 comparing a strategy of extubation in patients at high-risk of reintubation in ICUs. Patients will
40 randomly be assigned to one of the two groups performing SBT with T-piece or with pressure-
41 support, with a 1:1 ratio.
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46 47 **METHODS: PATICIPANTS, INTERVENTIONS AND OUTCOMES**

48 49 **Study setting**

50 The TIP-EX study is taking place in 31 ICUs in France. Patient flow chart is detailed in the **Figure**.
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53 54 **Eligibility criteria**

55 56 **Inclusion criteria**

57 Adult patients intubated more than 24 hours in ICU and at high-risk of reintubation will be eligible as
58 soon as possible once they meet all weaning criteria for an initial SBT.
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3 Patients will be considered at high-risk of extubation failure according to the following criteria⁹:
4 patients older than 65 years, or those having any underlying chronic cardiac or lung disease.
5 Underlying chronic cardiac diseases include left ventricular dysfunction (whatever the cause) defined
6 by left ventricular ejection fraction $\leq 45\%$, history of cardiogenic pulmonary oedema, documented
7 ischemic heart disease or permanent atrial fibrillation. Chronic lung diseases include any underlying
8 chronic obstructive pulmonary disease, obesity-hypoventilation syndrome (OHS) or restrictive
9 pulmonary disease. The underlying lung disease will be either documented or highly suspected by
10 the physician in a patient intubated for acute hypercapnic respiratory failure and having 1) a history
11 of smoking with intrinsic positive end-expiratory pressure during mechanical ventilation and/or
12 emphysema on chest X-ray or scanner suggesting underlying chronic obstructive pulmonary disease,
13 2) obesity (body-mass index $> 30 \text{ kg/m}^2$) with alveolar hypoventilation ($\text{PaCO}_2 > 45 \text{ mm Hg}$)
14 suggesting obesity-hypoventilation syndrome, or 3) rib cage deformation suggesting restrictive
15 pulmonary disease.

16 According to the international conference consensus on weaning,¹⁰ patients will be considered as
17 ready for an initial SBT as soon as they meet all the following criteria: a respiratory rate ≤ 35 breaths
18 per minute, adequate oxygenation defined as $\text{SpO}_2 \geq 90\%$ with $\text{FiO}_2 \leq 0.4$ or $\text{PaO}_2/\text{FiO}_2 \geq 150 \text{ mm Hg}$
19 with positive end-expiratory pressure $\leq 8 \text{ cmH}_2\text{O}$, hemodynamic stability with no need for
20 vasopressors (or minimal dosis $\leq 0.3 \mu\text{g/kg/min}$), adequate cough, patient awake with a Richmond
21 Agitation-Sedation Scale between +1 and -2.¹¹

22 Exclusion criteria

23 Patients fulfilling one of the following criteria will not be included: patients having already undergone
24 an initial SBT at any time since intubation, patients admitted for traumatic brain injury or with pre-
25 existing peripheral neuromuscular disease (underlying myopathy or myasthenia gravis), patients with
26 do-not-reintubate order at time of the initial SBT, patients previously included in the study, patients
27 without health insurance coverage, people under protection (pregnant or breastfeeding women,
28 minor patients, subjects with guardianship or under law protection), or refusal to participate.

29 Intervention

30 Spontaneous breathing trials before extubation

31 Patients included will be randomised before the initial SBT and assigned to one of the following 2
32 groups: 1) In patients assigned to control group all SBTs will be performed using T-piece; 2) In
33 patients assigned to experimental group all SBTs will be performed using PSV with a PS level of 8 cm
34 H_2O without positive end-expiratory pressure.

Control group: T-piece trial

The T-piece trial will be performed with a T-piece connected to the patient connection port of the endotracheal tube and providing additional oxygen (≤ 6 L/min). We will propose to add an oxygen flow rate of 3 L/min (oxygen blend) during the T-piece trial in patients mechanically ventilated with a FiO_2 0.3 prior to the T-piece trial and 6 L/min for those mechanically ventilated with a FiO_2 0.4.

Interventional group: PSV trial

The PSV trial will be performed without disconnecting the patient from the ventilator, by using a low level of pressure-support (PS of 8 cm H_2O) with a $\text{FiO}_2 \leq 40\%$ without positive end-expiratory pressure, and without activation of automatic tube compensation (ATC) mode, while continuously monitoring respiratory rate and tidal volume on the ventilator display.

Duration of treatment and strategy of weaning and extubation

In both groups, the SBT will be performed for around 1 hour according to weaning guidelines.¹⁰ In case of SBT success, patients will be systematically extubated the day of the trial. After a successful T-piece trial, patients will be reconnected to the ventilator with prior ventilatory settings for around 1-hour before extubation to avoid exhaustion. A previous study showed that a 1-hour period at rest under mechanical ventilation after SBT trial with T-piece may improve outcome.¹² We therefore decided to apply this protocol in our interventions.

In case of SBT failure, a once-daily SBT will be performed with the same method according to the assigned group (T-piece or PSV trial) every day as long as weaning criteria are met until SBT success and extubation. SBT failure will be defined according to the usual criteria from the international conference consensus on weaning,¹⁰ as development during the trial of any of the following events: (1) respiratory rate > 35 breaths/min, (2) increased accessory muscle activity, (3) SpO_2 persistently below 90% (or below 88% in case of underlying chronic lung disease) on $\text{FiO}_2 \geq 0.4$ or at least 6 L/min of oxygen, (4) hemodynamic instability defined as heart rate persistently above 140 beats / min, or systolic blood pressure < 90 or > 180 mmHg, with signs of hypoperfusion (appearance of cyanosis or mottling), (5) depressed mental status or agitation.

All patients will be followed until day 28 after the initial SBT. In the event of extubation failure and reintubation, weaning will then be performed with the same method according to the assigned group (T-piece or PSV trial). After extubation, prophylactic use of non-invasive ventilation alternating with high-flow nasal oxygen between non-invasive ventilation sessions will be recommended in all patients for at least 48 hours according to the results of the HIGH-WEAN study.^{13 14}

Outcomes

Primary outcome

The primary outcome is the number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28.

Secondary outcomes

Secondary outcome variables include the following:

1. The number of days alive and without mechanical ventilation (including intubation and non-invasive ventilation) between the initial SBT (day 1) and day 28.
2. The number of patients extubated within the 72 hours and within the 7 days following the initial SBT.
3. The number of patients extubated after simple (less than 24h), difficult (between 24 hours and 7 days) or prolonged (more than 7 days) weaning.
4. The number of patients extubated after the initial SBT and not reintubated within the following 72 hours.
5. The number of days between the initial SBT and the first extubation attempt.
6. The number of patients reintubated within the 72 hours and within the 7 days following extubation.
7. The number of patients with post-extubation respiratory failure within the 7 days following extubation.
8. Length of stay in ICU.
9. Mortality in ICU, at day 28 and at day 90.

Criteria for post-extubation respiratory failure

An episode of post-extubation respiratory failure will be defined by the presence of at least two criteria among the following: a respiratory rate above 25 breaths per minute, clinical signs suggesting respiratory distress with increased accessory muscle activity, respiratory acidosis defined as pH < 7.35 units and PaCO₂ > 45 mm Hg, hypoxemia defined as a need for FiO₂ at 50% or more to maintain SpO₂ level at least 92% or a PaO₂/FiO₂ ratio < 150 mm Hg.

Criteria for reintubation

To ensure the consistency of indications across sites and reduce the risk of delayed intubation patients will be immediately reintubated if at least one of the following criteria is fulfilled: severe respiratory failure, hemodynamic failure defined by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg with signs of hypoperfusion and serum lactate level greater than 2

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3 mmol/L, neurological failure (altered consciousness with Glasgow coma scale below 12), cardiac or
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5 respiratory arrest.

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7 Severe respiratory failure leading to reintubation will be defined by the presence of at least two
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9 criteria among the following: a respiratory rate above 35 breaths per minute, clinical signs suggesting
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11 respiratory distress with increased accessory muscle activity, respiratory acidosis defined as pH <
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13 7.25 units and PaCO₂ > 45 mm Hg, hypoxemia defined as a need for FiO₂ at 80% or to maintain SpO₂
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15 level at least 92% or a ratio of the partial pressure of arterial oxygen to the fraction of inspired
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17 oxygen (PaO₂/FiO₂) < 100 mm Hg.

18 **Sample size**

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20 We determined that enrolment of 900 patients would provide a power of 80% to show an absolute
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22 prolonged duration of mechanical ventilation by 2 days (number of ventilator-free days reduced by 2
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24 days) using the T-piece trial as compared to the PSV trial at a two-sided alpha level of 0.05.

25 **Expected number of patients to be included in the study: statistical justification**

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27 We calculated the number of patients to include based on results of our previous cohort.¹⁵ In this
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29 study, the number of ventilator-free days at day 28 among the 150 patients at high-risk for
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31 reintubation was 23 days (± 9) in mean, and all patients were extubated following a strategy of
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33 weaning using PSV trials. In the present study, a number of patients will never be extubated, *i.e.*
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35 either died or still under mechanical ventilation at day 28, and thus with no ventilator-free days.
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37 According to a recent large cohort study,⁴ these patients will represent around 2 to 3% of patients.
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39 Thus, we calculated that the number of ventilator-free days at day 28 would be 22 days (± 10) days
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41 using a PSV trial. In keeping with these results, we determined that enrolment of 786 patients would
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43 provide a power of 80% to show absolute prolonged duration of mechanical ventilation by 2 days
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45 (number of ventilator-free days reduced by 2 days) using the T-piece trial as compared to the PSV
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47 trial at a two-sided alpha level of 0.05. However, given the non-normal distribution of ventilator-free
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49 days in this population, the number of patients needed to be included was increased by 1.045 times
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51 in each group in order to compare the two groups with non-parametric tests.¹⁶ Therefore, we
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53 estimated that 820 patients will be needed. To ensure analysing at least 820 patients for primary and
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55 secondary outcomes taking into account of patients with withdrawal of consent or lost to follow-up,
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57 we decided to increase the number of inclusions by 10%, *i.e.* 900 patients in total (450 patients per
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59 group).

60 **Recruitment**

The expected initial duration of patient enrolment is 2 years, starting in January 2020.

- ▶ End of 2018: national grant award;
- ▶ 2019: approval by an independent ethics committee;
- ▶ 2020-2021: inclusion of patients (the first participant was enrolled the 31st January 2020)
- ▶ 2021-2022: end of inclusions, monitoring of participating centres and queries to investigators; blind review to determine protocol violation, to define intention-to-treat and per-protocol analysis populations; new queries to investigators, cleaning and closure of the database;
- ▶ 2022-2023: data analysis, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTION, DATA COLLECTION, MANAGEMENT AND ANALYSIS

Allocation and sequence intervention

After obtaining consent from the patient or his/her relative, all inclusion/exclusion criteria will be verified by the investigator before randomization. Before the initial SBT the investigator will randomize patients to determine the type of trial allocated (T-piece or PSV trial). Randomization will be stratified on centre and carried out by connecting to the electronic case report form (e-CRF) website <https://chu-poitiers.hugo-online.fr/CSOnline/> after fulfilling the “randomisation” page including all the criteria for eligibility.

Data collection and management

Data will be collected on an e-CRF by a trained investigator or research assistant at each centre. Patient follow-up and data collected are detailed in the study flow chart (**Table 1**).

Statistical methods

All the analyses will be performed by the study statistician according to a predefined statistical analysis plan and using statistical software (SAS, V.9.4; SAS Institute; USA). A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Descriptive analysis of patient groups at baseline

The analysis will be performed on an intention-to-treat basis after validation by a blind review committee of the inclusion/exclusion criteria for each patient. The continuous variables will be summarized with the classic parameters of descriptive analysis (median, interquartile ranges and extreme values or mean and standard deviation), while indicating the number of missing data. The category variables will be presented in the form of absolute frequency and percentage in each modality. Eligibility criteria will be verified on the basis of the data recorded in the case reports. Wrongly included subjects as well as those lost to follow-up will be described. Deviations from the protocol will be described and analysed on a case-by-case basis.

Analysis pertaining to the main criteria of evaluation

The number of ventilator-free days at day 28, defined as the number of days alive and without invasive mechanical ventilation (intubation or tracheostomy) between the initial SBT (day 1) and day 28, will be compared between the 2 groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate. A two-tailed P value of less than 0.05 will be considered as indicating statistical significance.

Analysis pertaining to the secondary criteria of evaluation

Extubation success and reintubation rates at the various pre-defined times, difficulty of weaning (simple, difficult or prolonged), post-extubation respiratory failure rates, and mortality will be compared between the 2 groups by means of the Chi2 test (or Fisher's exact test).

Weaning duration and lengths of stay will be compared between the two treatment groups by means of the Student's t-Test or the Mann-Whitney U test as appropriate.

Kaplan–Meier curves will be plotted to assess the probability of extubation from the initial SBT to the following 72 hours and to the following 7 days, the probability of reintubation from extubation to the following 72 hours and to the following 7 days, and the probability of death between the initial SBT until day 90, and will be compared by means of the log-rank test.

The variables associated with extubation success and reintubation with a p value <0.20 will be assessed by means of a multivariate logistic regression analysis or Cox proportional-hazard regression analysis using a backward-selection procedure as appropriate.

The final model will include variables significantly associated with intubation with a P value of less than 0.05 and will be expressed using adjusted relative risk and odds ratio or hazard ratio with 95% confident interval.

Predetermined Subgroup Analysis

Patients with prolonged duration of mechanical ventilation may have weaning difficulties and an increased risk of reintubation.^{4 15} Therefore, subgroups analyses will be performed for primary and secondary outcomes according to the duration of mechanical ventilation (> 7 versus ≤ 7 days) prior to the initial SBT after an interaction test carried out to detect heterogeneity of treatment effect between patients with a prior duration of mechanical ventilation of more than 7 days and the others.

Data monitoring

The trial will be overseen by a steering committee regarding the progression and monitoring of the study at REVA (Réseau Européen Ventilation Artificielle) Network meetings every 6 months.

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3 Research assistants from the coordinating centre will regularly monitor all the centres on site to
4 check adherence to the protocol and the accuracy of the recorded data. After being trained to
5 conduct the protocol and to fulfil the e-CRF, an investigator at each centre will be responsible for
6 daily patient screening, enrolling patients in the study, ensuring adherence to the protocol and
7 completing the electronic case-report form. Although the individual study assignments of the
8 patients cannot be masked, the coordinating centre and all the investigators will remain unaware of
9 the study group outcomes until the database will be locked.
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16 **ETHICS AND DISSEMINATION**

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18 The study has been approved by the central ethics committee (Ethics Committee Ile de France V,
19 Paris, France) with the registration number 2019-A02151-56 (07 October 2019).
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23 **Consent or assent**

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25 The patient will be included after having provided a written informed consent to the investigator
26 according to the decision of the central ethics committee. If the patient is not able to understand the
27 information given, he/she can be included if the same procedure is completed with a next of kin.
28 After the patient's recovery, he/she will be asked if he/she agrees to continue the trial.
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33 **Confidentiality**

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35 Data will be handled according to French law. Coding subjects will be done by recording the first
36 letter of the name and forename, accompanied by a single study identifier indicating the order of
37 subject inclusion, in order to store anonymized data in the e-CRF. The sponsor will ensure that each
38 study participant has given his/her consent for access to his/her personal data that is strictly required
39 for quality control of the study. All original records will be archived at trial sites for 15 years
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44 **Declaration of interest**

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46 The TIP-EX study is an investigator-initiated trial supported by the French Ministry of Health with
47 funds obtained in 2018 from a national hospital clinical research program (Programme Hospitalier de
48 Recherche Clinique National 2018). The study is promoted by the University Hospital of Poitiers.
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52 **Access to data**

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54 All investigators will have access to the final data set. Investigators will make available the
55 documents and individual data strictly required for monitoring, quality control and audit of the study
56 to persons having access to them, in accordance with the statutory and regulatory provisions in place
57 (articles L.1121-3 and R.5121-13 of the French Public Health Code).
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Dissemination policy

Findings will be published in peer-reviewed journals and presented at national and international meetings. Communications, reports and publication of the results of the study will be placed under the responsibility of the principal investigator-coordinator of the study and the executive committee. Rules of publication will follow the international recommendations according to *The Uniform Requirements for Manuscripts* (ICMJE, April 2010).

Patient and public involvement

Patients and public are not involved in the study

DISCUSSION

According to the physiological results,⁵ PSV trial is an easier test than T-piece trial and may potentially increase the risk of reintubation by underestimating the work of breathing needed after extubation.⁶ However, no study has demonstrated an increased reintubation rate using PSV trial as compared to T-trial.

Recently, a large randomised controlled trial including 1153 patients found that the proportion of patients successfully extubated 72 hours after the initial SBT was higher using a PSV trial for 30 minutes than using a T-piece trial for 2 hours.⁷ However, the proportion of patients with simple weaning (*i.e.* patients extubated after the initial SBT) was particularly high in this study (nearly 90%) whereas usual rates in the literature are closer to 60-70%.³ Moreover, patients with difficult weaning (*i.e.* those who failed the initial SBT) were not monitored up until extubation, thereby limiting application of these findings to simple weaning, and not taking into account patients with weaning difficulties.^{3 4} Lastly, reintubation rates were particularly low (around 11%) meaning that the population mainly included patients at low-risk of extubation failure.⁸ Although an easy test using PSV trial may hasten extubation, inclusion of patients at low-risk with reintubation rates around 10% or less might not enable to detect an increased risk of extubation failure. Therefore, to avoid underpowering the study and so as to be able to detect the risk, we decided to focus on patients at high-risk of extubation failure and to include patients with weaning difficulties. In this population at high-risk of reintubation a recent post-host analysis from a large randomised controlled trial showed that execution of an initial SBT using PSV significantly increased the proportion of patients successfully extubated within the following 72 hours as compared with T-piece.¹⁷ However, a large prospective clinical trial is needed to confirm these findings in this population before being in a position to apply this weaning strategy to all ICU patients.

To assess as primary outcome the duration of weaning on the one the hand and the risk of reintubation on the other hand, we decided to assess the number of ventilator-free days at day 28.

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3 This criterion has the advantage of evaluating the 2 end-points (duration of weaning and risk of
4 reintubation) with one and the same criterion. In previous studies, primary outcome was the number
5 of patients extubated after the initial SBT and not reintubated at 48h or 72h.^{7 18 19} Although this
6 outcome has weaknesses (too early and focusing only on simple weaning), we will also assess the
7 number of patients extubated after the initial SBT and not reintubated within the following 72h, in
8 order to compare our results to previous studies. Lastly, as performing a T-piece or PSV trial may
9 influence the success of the initial SBT and duration between the initial SBT and successful
10 extubation, we will compare the proportion of patients with simple, difficult and prolonged weaning
11 according to type of SBT. Simple weaning includes patients extubated within the first 24 hours after
12 the initial SBT, difficult weaning includes patients extubated between 24 hours and 7 days after the
13 initial SBT, and prolonged weaning includes patients extubated more than 7 days after the initial
14 SBT.⁴

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16 No risk is expected with these 2 SBTs, as both of them are routinely and daily performed in the
17 clinical practice of participating centers. Type of SBT may modify only the physician's decision of
18 extubation, and no other treatment will be added or modified.

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20 In conclusion, the TIP-EX trial is an investigator-initiated pragmatic randomised controlled trial
21 empowered to test the hypothesis that SBTs performed using PSV may hasten extubation without
22 increasing the risk of reintubation in patients at high-risk of extubation failure as compared to T-
23 piece. These 2 strategies have never been compared in patients at high-risk of reintubation, and
24 therefore, this large trial may help to establish strong recommendations with a high level of evidence
25 on a daily clinical practice for extubation in ICUs.

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For peer review only

Table 1: Study flow chart

Procedures and assessments	From inclusion to the initial SBT	From the initial SBT to extubation	From the initial SBT to day 28	Until ICU discharge and day 90
Inclusion and non-inclusion criteria	X			
Information and consent	X			X
Randomisation	X			
Characteristics of the patient ¹	X			
Characteristics of the initial SBT ²	X			
Characteristics at time of extubation ³		X		
Characteristics after extubation ⁴			X	
Vital status				X

(1) Characteristics of the patient include age, gender, height, weight, severity score indicated by the Simplified Acute Physiological Score (SAPS) II and the Sepsis-related Organ Failure Assessment (SOFA) score, underlying chronic cardiac or respiratory disease, date and reason for admission/ intubation, duration of intubation prior to the initial SBT, ventilatory settings and blood gases before the initial SBT.

(2) Characteristics of the SBT include duration, type and settings of the initial SBT, vital parameters at the end of the initial SBT, and criteria for SBT failure.

(3) Characteristics at time of extubation include duration of weaning between the initial SBT and extubation, the number of SBTs attempts before extubation, classification according to the weaning difficulty, administrations of steroids before extubation, qualitative assessment of cough strength and amount of secretions at time of extubation.

(4) Characteristics after extubation include the use and duration of non-invasive ventilation and high-flow nasal oxygen after extubation (as well prophylactic use as rescue therapy to treat post-extubation respiratory failure), criteria for post-extubation respiratory failure, criteria for reintubation, need for reintubation, number of days of mechanical ventilation (invasive and non-invasive), tracheostomy, and death.

FIGURE LEGEND

Figure 1: Flow chart of the patients and study design.

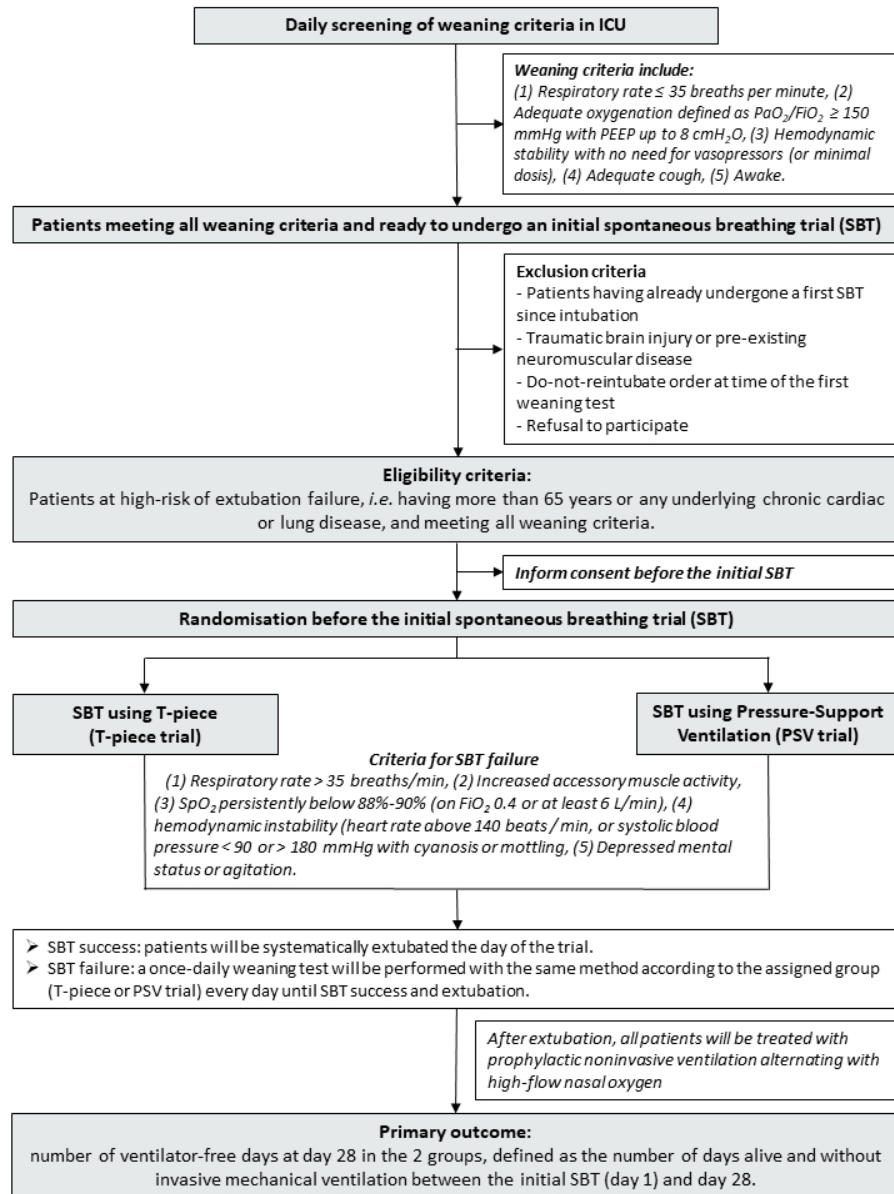


Figure 1: Flow chart of the patients and study design.

190x254mm (96 x 96 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item; No: Page	Description
Administrative information		
Title	1: Page 1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a: Page 3	Trial identifier and registry name. If not yet registered, name of intended registry
	2b: Page 3	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4: Page 3	Sources and types of financial, material, and other support
Roles and responsibilities	5a: Page 1-3	Names, affiliations, and roles of protocol contributors
	5b: Page 3	Name and contact information for the trial sponsor
	5c: NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d: Page 14	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a: Page 6	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b: Page 6	Explanation for choice of comparators
Objectives	7: Page 6-7	Specific objectives or hypotheses

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2	Trial design	8: Page 7	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
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8	Methods: Participants, interventions, and outcomes		
9			
10	Study setting	9: Page 7	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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14	Eligibility criteria	10: Page 7-8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
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19	Interventions	11a: Page 8-9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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22		11b: Page 9	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
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26		11c: Page 9	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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31		11d: Page 9	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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34	Outcomes	12: Page 9-10	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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42	Participant timeline	13: Page 9-10	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
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47	Sample size	14: Page 11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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51	Recruitment	15: Page 111	Strategies for achieving adequate participant enrolment to reach target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a: Page 12	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
3	generation		
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10	Allocation	16b: Page 12	
11	concealment		
12	mechanism		
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15	Implementation	16c: Page 12	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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18	Blinding	17a: Page 12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
19	(masking)		
20		17b: Page 12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

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30	Data collection	18a: Page 12	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
31	methods		
32			
33		18b: Page 12	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
34			
35		19: Page 12	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
36	Data		
37	management		
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40		20a: Page 12-13	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
41	Statistical		
42	methods	20b: Page 12-13	Methods for any additional analyses (eg, subgroup and adjusted analyses)
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20c: **Page 12-13** Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a: **Page 13** Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

21b: **Page 13** Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22: **Page 13** Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23: **Page 13** Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval 24: **Page 14** Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25: **Page 14** Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a: **Page 14** Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b: **Page 14** Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27: **Page 14** How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28: **Page 14** Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29: **Page 14** Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	31a: Page 14	Plans for investigators and sponsor to communicate trial results
6	policy		to participants, healthcare professionals, the public, and other
7			relevant groups (eg, via publication, reporting in results
8			databases, or other data sharing arrangements), including any
9			publication restrictions
10			
11		31b	Authorship eligibility guidelines and any intended use of
12			professional writers
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14		31c	Plans, if any, for granting public access to the full protocol,
15			participant-level dataset, and statistical code
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19	Appendices		
20			
21	Informed consent	32: model	Model consent form and other related documentation given to
22	materials	consent form	participants and authorised surrogates
23		available in	
24		supplementary	
25		files	
26			
27	Biological	33: NA	Plans for collection, laboratory evaluation, and storage of
28	specimens		biological specimens for genetic or molecular analysis in the
29			current trial and for future use in ancillary studies, if applicable
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32 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013

33 Explanation & Elaboration for important clarification on the items. Amendments to the

34 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

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