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REVIEW ARTICLE

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Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents III: The 2023 Geneva revision

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Abstract

The set of guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents was developed following an international consensus conference in Copenhagen in 1996 (Viby-Mogensen et al., *Acta Anaesthesiol Scand* 1996, **40**, 59–74); the guidelines were later revised and updated following the second consensus conference in Stockholm in 2005 (Fuchs-Buder et al., *Acta Anaesthesiol Scand* 2007, **51**, 789–808). In view of new devices and further development of monitoring technologies that emerged since then, (e.g., electromyography, three-dimensional acceleromyography, kinemyography) as well as novel compounds (e.g., sugammadex) a review and update of these recommendations became

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necessary. The intent of these revised guidelines is to continue to help clinical researchers to conduct high-quality work and advance the field by enhancing the standards, consistency, and comparability of clinical studies.
There is growing awareness of the importance of consensus-based reporting standards in clinical trials and observational studies. Such global initiatives are necessary in order to minimize heterogeneous and inadequate data reporting and to improve clarity and comparability between different studies and study cohorts. Variations in definitions of endpoints or outcome variables can introduce confusion and difficulties in interpretation of data, but more importantly, it may preclude building of an adequate body of evidence to achieve reliable conclusions and recommendations. Clinical research in neuromuscular pharmacology and physiology is no exception.

KEYWORDS
depth of neuromuscular blockade, neuromuscular monitoring, neuromuscular research, pharmacodynamics, postoperative pulmonary complications, time course of neuromuscular blockade

Editorial Comment

This overview article presents a detailed update of earlier expert group statements concerning good practice for studying effects of neuromuscular blocker effects. The article included both details concerning study design and also intricacies for studying neuromuscular blockade effects. All with an aim to improve quality for clinical investigations in this area of study.

1 | CLASSIFICATION OF CLINICAL TRIALS

Clinical trials of new drugs are generally classified into Phase I, II, III, and IV studies. However, it is not always possible to draw a distinction between the individual phases as there may be diverging opinions about the definitions. In addition, Phases II and III may have early and late phases.

The following definitions are found in the European Union guidelines.[3]

1.1 | Phase I

The first trials of a new active substance in man are often carried out in healthy volunteers. The purpose is to establish a preliminary evaluation of safety and the pharmacodynamic and pharmacokinetic profiles. The agents are often administered initially in small doses with later dose escalation. The subjects in Phase I trials have no therapeutic indication for the drug.

1.2 | Phase II

These are the first clinical studies in patients with an indication for the use of the new agent under investigation. The purpose is to demonstrate both the efficacy and the safety of the agent. The trials are performed in a limited number of subjects and may initially include placebo controls but include active comparators at a later stage. This phase also often involves blood sampling for safety and pharmacokinetic analysis. It is usually in this phase that the appropriate dose ranges/regimens and, if possible, dose–response relationships are established.

1.3 | Phase III

Phase III trials are carried out in larger and possibly varied groups of patients including different age groups. Any possible interactions are also studied at this time. The trial at this stage will usually be randomized and double-blind and include a comparator group.

1.4 | Phase IV

Phase IV studies are performed after the licensing and marketing of the final medicinal product. These are also sometimes referred to as post-marketing studies.

Readers can get more information about the phases of clinical trials from:

European Medicines Agency (EMA): https://www.ema.europa.eu/en/human-regulatory/research-development or

US Food and Drug Administration (FDA): https://www.fda.gov/patients/clinical-trials-what-patients-need-know/what-are-different-types-clinical-research

or

National Institutes of Health: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

2 | INTERNATIONAL STANDARDS ON THE PERFORMANCE AND REPORTING OF CLINICAL RESEARCH

There are certain rules, recommendations, and guidelines that apply to all types of clinical research. These rules also apply to pharmacodynamic studies of neuromuscular blocking agents (NMBAs) although these are not specifically discussed in this paper. The readers' attention is drawn to some of the more important ones: The Helsinki Declaration, which deals with ethical conduct in research studies in humans[4]; the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) site that contains a comprehensive searchable database of reporting guidelines and links to resources relevant to research reporting (https://www.equator-network.org); the CONSORT-statement, dealing with evidence-based standards to ensure the quality of randomized controlled trials (http://www.consort-statement.org/); and the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" made by the International Committee of Medical Journal (ICMJ) Editors (http://www.icmje.org/). These recommendations and guidelines provide the ethical principles for reporting research and make recommendations for preparing manuscripts. The requirements are a prerequisite for most biomedical journals before a study is accepted for publication.

According to the ICMJ, a trial will only be considered for publication if it has been registered prior to the opening to enrollment of participants in the study. This policy applies to all human clinical trials that have started enrolling after July 1, 2005. Trials can be registered at http://www.controlled-trials.com/, https://www.who.int/clinical-trials-registry-platform, or http://clinicaltrials.gov/, among others.

The investigators must follow the guidelines on trials of medicinal products in humans as described in the ICH Harmonized Tripartite Guideline encompassing the "Guideline for Good Clinical Practice."[5]

3 | REPORTING GUIDELINES FOR STUDIES ON NMBAs

The guidelines suggested in Table 1 are for Phases I and II studies, while those in Table 2 are for Phases III and IV, and for other clinical studies.

3.1 | Patient characteristics, anesthesia, and test drug administration

Many factors influence the reported effects of NMBAs. The most important are age, medical condition (ASA physical status classification), sex, body weight (BW), anesthetic technique, and the method of monitoring used. During anesthesia, several drugs are used simultaneously and among these, volatile halogenated anesthetic agents are well known to enhance the magnitude and duration of neuromuscular block. Some intravenous agents may also affect neuromuscular blockade, as may neuromuscular, liver, or renal disorders, and some concomitant medications.[6]

TABLE 1 Guidelines for Phases I and II studies.

	Preferred standards	Variables that should be reported
Patients	Age 18–65 years ASA physical status I or II Weight (Kg) BMI 18.5–24.9 Sex distribution Exclusion criteria: - Patients having concurrent disease - Patients taking concurrent medications - Major surgery associated with massive blood loss or fluid replacement Number and reasons for exclusion of patients originally included in the study Number and reasons for exclusion of data points	Number of patients Ethnicity Height Surgical procedure Relevant laboratory data Location of i.v. catheters Location of blood pressure cuff in relation to monitoring equipment BMI outside 18.5–24.9 range
Anesthesia	Intravenous anesthesia Avoidance of potent volatile anesthetics	Nitrous oxide
Test drug administration	Drug dose calculated according to actual body weight Duration of drug injection: 5 s (20 mL saline flush)	Injection speed may vary according to drug and protocol
Equipment and Nerve Stimulation	Mechanomyography (or electromyography) TOF stimulation or 0.1 Hz single twitch stimulation of ulnar nerve with a recording of the response at adductor pollicis muscle Monitor placed on the arm opposite to BP cuff	Acceleromyography

TABLE 2 Guidelines for Phases III, IV, and other clinical studies.

	Preferred standards	Variables that should be reported
Patients	Age using the following age groups: - Neonates <1 month - Infants 1 month to 1 year - Children 2–11 years - Teenager 12–17 years - Adults 18–64 years - Elderly 65–79 years - Oldest-old >80 years Weight BMI 18.5–24.9 Sex distribution (M:F) Exclusion criteria: - Patients with interfering disease - Patients taking interfering drugs Number and reasons for exclusion of patients originally included in the study Number and reasons for exclusion of individual data points originally included in the study	Number of patients Ethnicity Height ASA physical status Type of anesthesia Surgical procedure Relevant laboratory data Location of i.v. catheters Location of blood pressure cuff in relation to monitoring equipment BMI outside 18.5–24.9 range Concomitant drug treatment Renal disease Hepatic disease Neuromuscular disease Enzymatic disorder
Anesthesia	Intravenous or volatile anesthesia	End-tidal concentration of volatile anesthetics, nitrous oxide
Test drug administration	Drug dose calculated according to actual body weight Duration of drug injection: 5 s	Injection speed may vary according to drug and protocol
Equipment and nerve stimulation	Mechanomyography, electromyography, or acceleromyography, although acceleromyography results are not interchangeable with electromyography or mechanomyography TOF stimulation or 0.1 Hz single twitch stimulation of the ulnar nerve with a recording of the response at the adductor pollicis muscle Stable control response for 2 min and stable temperature Baseline established in anesthetized patients before administration of muscle relaxant (see Table 3).	Site of monitoring
General design	Comparative design when relevant randomization and blinding if appropriate (describe the method of randomization)	Double blinding preferred

3.1.1 | Age

Initial clinical trials (Phase I and II studies) should be performed in adults aged 18–65 years. Phases III and IV studies are usually performed in different age groups, preferably using the age groups described in Table 2. According to the World Health Organization guidelines, the term, "elderly" is defined as greater than 65-years-old, and "oldest-old" is defined as greater than 80-years-old. Most clinical guidelines recommend that patients older than 70 years be included in investigations,[7,8] especially since pharmacodynamic and pharmacokinetic data from the oldest-old are still missing in the literature. For the sake of uniformity, an arbitrary age of over 65 years may be considered as the lowest age for the elderly, but it is recommended to have a clear age gap (e.g., 10 years) when comparing adults with the elderly or elderly with the oldest-old adults. Moreover, specific pharmacodynamic and pharmacokinetic data from octogenarians and nonagenarians are needed.

3.1.2 | Sex

The potential biological impact of sex should be taken into account when the study is designed. Sex can influence both the pharmacodynamic and the pharmacokinetic responses to NMBAs and their antagonists and should therefore be recorded.[9]

3.1.3 | Weight

BW varies with age, sex, and type of body composition.[10–12] It is important to relate the BW to the height, otherwise, both thin (and short) and obese (and tall) patients may be included as normal BW. The body mass index [BMI; calculated as BW (in kg) divided by height^2 (in m^2)] should be used to categorize patients; however, the dose of drugs to be administered is often based on patient's actual body weight (ABW).[13] The method used for calculating the dose of administered NMBA and antagonists should be specified (e.g., actual, ideal, or lean BW).

A BMI calculator is available at: https://www.cdc.gov/healthyweight/bmi/calculator.html.

3.1.4 | Co-existing disease

In Phases I, II, and early Phase III studies, patients with intercurrent disease or receiving concurrent medication should be excluded

TABLE 3 The categorization of adult patients based on their BMI should be as follows.

Category	Body mass index (BMI) in kg/m^2
Severe thinness	<16.0
Underweight	<18.5
Normal range	18.5–24.9
Overweight	>25.0
Obesity	>30.0
Morbid obesity	>40.0

(Table 1). In later Phase III studies, these patients may be included, but intercurrent disease or the medication being taken should be detailed.

3.1.5 | Anesthesia techniques

To ensure consistency among studies, the use of intravenous anesthetics for induction and maintenance (which may include opioids) are recommended in Phases I and II studies of NMBAs and their antagonists. It should be stated whether nitrous oxide has been used. In later phases, studies should be performed with different anesthetic techniques (e.g., inhalational) in order to evaluate the potential of any drug interactions, such as potentiation of neuromuscular block. Throughout the period of a study, the depth of anesthesia should be constant, as much as possible, as factors such as depth of volatile anesthesia and underlying muscle tone may impact the measured depth of block.

3.2 | Standards common to all types of neuromuscular monitoring

Regardless of method used for neuromuscular monitoring, standard procedures should be followed to obtain reliable and comparable results. The most important minimal standards are given in Table 4.

3.2.1 | Skin preparation and stimulation electrodes placement

Properly cleansed skin rubbed with an abrasive, is a prerequisite to achieving supramaximal stimulation with surface electrodes. Correct placement of electrodes is important to ensure that the nerve is stimulated with the selected current (Figure 1). The size of the conducting area of the stimulating electrodes is also important. With a large conducting area, it may be difficult or impossible to obtain supramaximal stimulation because sufficient current density cannot be obtained in the nerve underlying the stimulating electrode. Typically, the contact area of the stimulating electrode should be 7–11 mm in diameter. The distance between the centers of the two electrodes should be 3–6 cm. Finally, while the polarity of the stimulating electrodes is also important, and it is recommended that the negative electrode be placed distally to optimize nerve stimulation response.[14]

3.2.2 | Stimulation patterns

The response to nerve stimulation depends on the frequency with which the individual stimuli are applied. Stimulus patterns that historically have been regarded as interchangeable [e.g., 0.1 Hz single twitch (ST) vs. train-of-four (TOF) stimulation every 12 s] produce different pharmacodynamic data.[15–20] Therefore, it should be stated whether a 0.1 Hz ST stimulation or a 2-Hz TOF stimulation for 1.5 s repeated every 12 s (or more) has been applied. Moreover, the time used to achieve a stable control response may influence the subsequent determination of the onset time and duration of block.[21] In general, the use of increased stimulus frequency will lead to an interpretation of shorter onset time of non-depolarizing NMBAs and prolonged duration of action. The duration (pulse width) of the individual stimuli should be 300–400 ms or less to avoid repetitive nerve firing and direct muscle stimulation. The response to post-tetanic count (PTC) stimulation may depend on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first post-tetanic stimulus, the frequency of ST stimulation, and the duration of 1 Hz stimulation before the tetanic stimulation.[22,23] These variables should be kept constant and reported.

3.2.3 | Temperature

While changes in core temperature affect the pharmacodynamics and pharmacokinetics (PK/PD) of NMBAs, changes in peripheral temperature at the neuromuscular monitoring site may affect the response to nerve stimulation. It is therefore recommended to monitor both the core and peripheral skin temperatures at the monitoring site, which should be kept above 35°C and 32°C, respectively.[23–27]

3.2.4 | Supramaximal stimulation

When a nerve is stimulated with sufficient current intensity, all muscle fibers supplied by the nerve will contract, and the maximum response (muscle contraction) will be triggered. To ensure that a decrease in muscle response after injection of the NMBA is caused by the drug and not by a decrease in the number of fibers being activated (due to a decreasing current or an increase in skin impedance), the stimulus must be maximal throughout the period of monitoring. This applies irrespective of the method of measurement used. In order to account for potential increases in the requirement for current intensity, the stimulating current (in milliamperes, mA) applied is usually 15%–20% above the current needed to produce a maximal stimulation and muscle response, and it is termed supramaximal stimulus.

The intensity of the stimulus depends on both the current intensity (in mA) and the duration of the stimulation (pulse width, in milliseconds, ms). These two parameters (current intensity and stimulus duration) determine the total charge (in µCoulombs, µC) delivered to the nerve (electrical charge = current intensity × pulse duration). Thus, a stimulus of 40 mA of 0.2 ms duration will have a total charge of 8 µC. It appears that at the same total charge, a higher current

TABLE 4 Standards common to all types of neuromuscular monitoring.

Procedure	Preferred standards	Variations that should be reported
Skin preparation	Clean, dry, degreased, and abraded	
Stimulating electrodes	Type of electrode (surface) Contact area: 7–11 mm in diameter Electrode placement: 3–6 cm apart	Placement of negative electrode if location other than distal to positive electrode
Electrode curing time	Preferably >10 min	Describe curing time if <10 min
Monitoring site	Ulnar nerve/adductor pollicis muscle	Any other monitoring sites (describe stimulated nerve and recording muscle sites)
Stimulation patterns	Stimulus duration: 200 μs, square wave, biphasic pattern TOF: 2 Hz for 1. 5 s repeated every ≥12 s 0.1 Hz: single twitch stimulation every 10 s PTC: 50 Hz stimulation for 5 sec followed by a 3-s delay and 20 single twitch stimulations at 1 Hz Each PTC recording is separated by ≥2 min DBS3,3: three impulses at 50 Hz frequency repeated after a 750-ms interval by another three impulses at 50 Hz	100–300 μs Any other stimulation patterns (including DBS3,2) Interval between trains of stimuli Interval between PTC stimulations if other than every 2 min
Initial signal stabilization	Immobilization and preload, when relevant Supramaximal stimulation: defined as current resulting in maximal response, plus 20%–30% current increase (in mA) Definition of control response: variability of less than 5% for at least 2 min before administration of the muscle relaxant obtained with the same stimulation mode to be used subsequently	Supramaximal stimulation level checked at the end of experiment Comparison of final twitch amplitude to that of the baseline single twitch
Documentation of stable recovery	Stable recovery of the signal should be documented Return to control value is defined as stable T1 value between 80%–120% and TOF ratio ≥0.9 and response variation <5% for 2 min All recorded T1 values for a neuromuscular block should be "normalized" to the final T1 value	The magnitude of drift in T1 should be documented Any excluded data should be described
Temperature	Central ≥35°C Peripheral skin temperature at the monitored muscle ≥35°C measured with a surface probe	Tympanic membrane, rectal or esophageal
Mechanical ventilation	End-tidal CO_2 or $PaCO_2$ measurement Provide a definition of normoventilation	
Inhalational anesthetics	Provide end-tidal concentration and duration of exposure	Choice of inhalational anesthetic agent

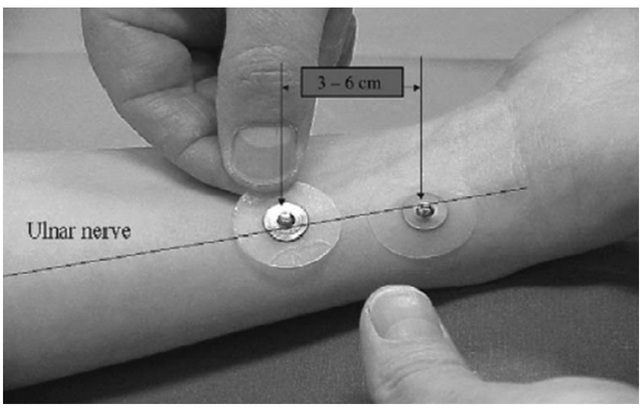

FIGURE 1 Stimulating electrodes with appropriate contact area in correct position over the ulnar nerve of the left forearm.

amplitude (e.g., 60 mA, 0.2 ms) may evoke a slightly larger muscle response than a longer pulse width (40 mA, 0.3 ms) (Table 5).[14]

The maximum current delivered by the commercially available nerve stimulators is limited to 60–80 mA (pulse width of 0.2–0.3 ms) for safety reasons. A stimulus duration of 0.2 ms (200 μs) is the recommended standard, although a longer duration (i.e., 0.3 ms) may be used to achieve the current necessary for supramaximal stimulation. Some EMG-based monitors employ a stimulating current duration (pulse width) of 0.1 ms. The duration of the impulses should not exceed 0.3–0.4 ms to avoid repetitive firing and the likelihood of direct muscle stimulation.[28,29] Careful placement of appropriate electrodes and skin preparation are essential to achieve supramaximal stimulation (see the section on skin preparation and stimulation electrodes placement). It may not be possible to achieve supramaximal stimulation if the electrodes are placed too

TABLE 5 Acceleromyographic responses.

Amplitude of evoked responses[a] (% of control) Position/polarity orientations							
Current (mA)	Pulse width (ms)	Charge (μQ)	A−	A+	B−	B+	Significance (p < .05)
20	0.2	4	12	8	25	21	b
	0.3	6	29	16	38	33	c
40	0.2	8	54	45	55	71	
	0.3	12	79	70	65	81	b
50	0.2	10	80	77	66	85	b
	0.3	15	101	96	98	101	
60	0.2	12	100	100	100	100	
	0.3	18	119	111	117	120	

Note: From: Brull and Silverman DG.[14]
[a]Amplitude of evoked response as % amplitude that was obtained at 60 mA, 0.2 ms in each of the four configurations.
[b]p < .05, A− versus B−.
[c]p < .05, A− versus A+.

far from the nerve or if there is too much insulating adipose tissue between nerve and stimulating electrodes. How supramaximal stimulation is achieved should be described in any study where supramaximal stimulation is used.

Some newer monitors operate with an alternative option to ensure maintenance of a maximum stimulus by directly measuring the skin impedance (resistance). If the skin resistance remains within the prespecified parameters, stimulation of the nerve is assured with the selected electrical current. Using these devices there is no need to determine supramaximal current.

Submaximal stimulation (e.g., using a current of 25–30 mA) may be of use in unanesthetized or lightly sedated patients. This method has the advantage of being less painful than using supramaximal currents and has been used for measurement of TOF ratios in the postoperative period. Stimulation with submaximal currents (e.g., 20, 30 mA) produces less discomfort than stimulation with 50 mA current, and the TOF ratios (as well as double burst ratios) remain consistent,[30,31] particularly if the current amplitude is >25 mA above the threshold for stimulation.[32] However, the accuracy of monitoring is less than with supramaximal stimulation, and the use of supramaximal current is recommended.

3.2.5 | Calibration

Before administration of the NMBA, calibration of the device is a prerequisite for obtaining reliable and reproducible data. For acceleromyographic monitors, calibration requires that the gain be adjusted to obtain a twitch height of 100% using a ST mode of stimulation, or of T1 when using a TOF mode of stimulation. As all four responses after TOF stimulation are amplified equally by calibration, the TOF ratio is not influenced by the procedure. Calibration increases the likelihood that the responses will be within the measurement window and decreases the risk of significant background noise. As the calibration procedure varies with the type of device used, it should always be described in detail.

3.2.6 | Signal stabilization

It is important to have a stable control (baseline) response, that is, less than 5% variability in the amplitude of the response to nerve stimulation for at least 2 min, using the same stimulation rate and pattern as planned for the study, prior to administration of the NMBA. The duration of signal stabilization should be documented. The time necessary to achieve this stable control response depends on both the duration of the stimulation and on the frequency of the stimulation with which the individual stimuli are applied. When using 0.1 Hz ST or TOF stimulation every 12 or 15 s, it may take 5–20 min to achieve a stable response. However, the stabilization period may be shortened by applying a short high-frequency stimulation. Thus, 50-Hz tetanic stimulation for 5 s shortens the stabilization period to 2–5 min.[33,34]

The response should be stable (less than 5% variation) for at least 2 min before NMBA administration, using the same stimulation rate and pattern as planned for the study. Any change in stimulus pattern using acceleromyography (AMG) and mechanomyography (MMG) after stability has been achieved is likely to result in a change in the twitch height amplitude. This effect is less pronounced with EMG, although EMG amplitude may increase by 2%–3% per °C decrease in the surface temperature, while the integrated EMG area may vary by 4%–8% per °C.[35,36] For these reasons, studies using EMG monitoring should specify the method for quantification of the compound muscle action potential (cMAP) (i.e., integrated area vs. amplitude vs. duration of cMAP).

The following sequence describes how calibration, supramaximal stimulation, and stable baseline may be achieved when using MMG or AMG before administration of NMBA:

1. Apply a few (3–5) stimulations (ST or TOF, using 40–50 mA).
2. Apply a 50-Hz tetanic stimulation for 5 s (for MMG and AMG monitors)—EMG is less prone to baseline drift.[37]
3. Adjust twitch height to 100% (calibration) when using AMG monitors, if available.

4. Ensure supramaximal stimulation current (increase current amplitude, pulse duration, or both).
5. Start the stimulation pattern and rate to be used in the study.
6. Recalibrate if twitch height deviates from 100% by more than 5%.
7. Is a stable baseline for 2–5 min achieved?
    - Yes: administer NMBA.
    - No: check the equipment, repeat the set-up procedure, and start again from “step 3.”

3.2.7 | Immobilization

All methods of neuromuscular monitoring are sensitive to movement to varying extent. Proper immobilization of the relevant extremity (e.g., the arm and the fingers when the ulnar nerve is stimulated) is, therefore, mandatory when using MMG or AMG; EMG is less prone to movement artifacts. Whether the monitored muscle (e.g., adductor pollicis) should be fixed as well depends on the method used (see the section on Equipment). The blood pressure cuff should not be applied to the limb being used for neuromuscular monitoring to avoid any effect on the signal quality and venous blood drug delivery. For these reasons, monitors that use blood pressure cuff inflation as a technique for monitoring neuromuscular evoked responses (e.g., TOFcuff, RGB Medical Devices S.A., Madrid, Spain) should not be used in PK/PD studies.

3.2.8 | Direct muscle stimulation

A muscle may contract in response to direct muscle stimulation as opposed to indirect (nerve) stimulation. However, direct muscle stimulation requires a stimulus that is significantly greater than that required for nerve depolarization. Direct muscle stimulation is probably unlikely to occur with low current (≤ 40 mA) and short pulse durations (≤0.2 ms).[28,29] Although infrequent, this direct muscle stimulation may occur when using ulnar nerve stimulation at the wrist. In practice, direct muscle stimulation is characterized by the fact that the ST or TOF response does not disappear during deep or intense blocks. In addition, the muscle responses are generally smaller and exhibit little or no fade in the response to stimulation during neuromuscular block. Direct muscle stimulation may sometimes disappear when the location of the stimulating electrodes is changed to one closer to the nerve. Persistent background noise or direct muscle stimulation (if present) should be reported. If direct muscle stimulation and/or background noise appear stable, the observed twitch responses may be adjusted before analysis by subtracting the small amplitude of such responses from all observed twitches (changing the signal-to-noise ratio). Such adjustments (if carried out) should be reported.

3.3 | Equipment

For many years, MMG has been considered the “gold standard” (reference method) for quantification of neuromuscular block. However, the method has not undergone any development for several decades and is now used infrequently outside the few research centers that have built their own mechanomyographs. At present, EMG and AMG are replacing MMG in research use. If available, MMG could be considered as the comparator when new neuromuscular monitoring technologies are being evaluated. Alternatively, established devices that are based on other measurement techniques (such as AMG or EMG) could be used as a comparator in validation studies.

3.3.1 | Mechanomyography

MMG measures isometric muscle contractions (force of contraction) in response to nerve stimulation. Table 6 shows the standards proposed for neuromuscular research using MMG.

The method is somewhat cumbersome and is therefore never used in routine clinical practice. It requires a preload, an immobilized

TABLE 6 Guidelines for mechanomyographic (MMG) monitoring.

Equipment/ procedure	Preferred standards	Variations that should be reported
Transducer	Document the following data: - Linearity of response - Response time - Stability over time Transducer should match patient characteristics	None
Signal quantification	Maximum amplitude of force response	None
Signal stabilization	Transducer firmly fixed Isometric conditions Preload of 200 gm in adult patients	After achieving supramaximal stimulation level, the preload should be readjusted before response measurement Preload of 100–300 gm Preload should be checked and adjusted regularly during the procedure only when outside the 100–300 gm range
Amplifier characteristics	Documentation of signal-to-noise (S/N) relationship Continuous display and recording of twitch responses	The recording should provide an original signal using original data, or the data should be analog-to-digital converted for direct computer analysis

Note: See all standards common to all types of neuromuscular monitoring.

limb, and a firmly fixed force transducer, and is very sensitive to movement.[38] The most commonly used muscle for recording MMG responses is the adductor pollicis, but other muscles such as the hallucis brevis and laryngeal adductor muscles have also been used. However, the responses from these alternative muscles cannot be used interchangeably with adductor pollicis responses and therefore are not suitable for use in pharmacodynamic studies of NMBAs.

3.3.2 | Electromyography

Since EMG and MMG measurements correlate well,[39,40] EMG use is preferable to AMG (and KMG) when MMG is not available, although any modality may be used and reported. Evoked EMG records the compound muscle action potential using recording electrodes after stimulation of the corresponding nerve. It allows online analysis and graphical display of the evoked response. The rationale behind the preferential use of EMG monitoring of neuromuscular block is the fact that changes in force of contraction of a muscle (MMG) are proportional to the changes in the compound muscle action potential (EMG). Thus, alterations in electromechanical coupling such as in hemiplegia, may limit the performance of MMG, but not the performance of EMG.

The EMG method uses less cumbersome equipment, is easy to use in small children, and makes it feasible to monitor responses from muscles inaccessible to mechanical monitoring.[41] Although many sites have been used, the most common ones for recording the EMG signal are the thenar eminence (adductor pollicis m), the hypothenar eminence (abductor digiti minimi m), and the space between the first and second metacarpals on the dorsal side of the hand (first dorsal interosseous m). A description of the precise location of the recording electrodes is mandatory because these hand muscles do not always generate identical data. Careful skin preparation will improve the quality of the EMG recording and reduce the risk of artifacts. Ag/AgCl electrodes with a recording diameter of 0.7–1.1 cm are normally used. It is not known whether the duration of stabilization influences the skin-electrode interface during recording, but skin curing time necessary for effective nerve depolarization via the gel electrodes may require 10–15 min.[42]

Both inspection of the EMG signal and the criteria for an acceptable response are important. Ideally, the EMG response should have a two-phase profile with a well-defined initial upward (negative) deflection not influenced by stimulation artifacts. Amplitudes are in the range of 5 mV for the hypothenar muscle to 20 mV for the first dorsal interosseous muscle. EMG area under the curve and amplitude appear to reflect neuromuscular transmission equally.[43] The principal disadvantage of EMG monitoring is the signal drift which may partly be a function of hand temperature.[44] However, the drift (approximately 2%–8% decrease in T1 height per °C increase) can be compensated for by normalization of the twitch height value after the temperature is stabilized.[35,44] Although the temperature affects the twitch height (T1), the TOF ratio is not affected.[43] This lack of effect of temperature on the EMG TOF ratio is unlike the marked TOF ratio depression of 20% per °C temperature decrease seen with MMG.[45] Manufacturers' recommendations for monitor setup should be followed.

Guidelines for EMG monitoring are given in Table 7. See also a section on Standards common to all types of neuromuscular monitoring.

3.3.3 | Acceleromyography

The acceleromyographic method of monitoring neuromuscular block is based on Newton's second law of motion: force = mass × acceleration.[46]

TABLE 7 Guidelines for electromyographic (EMG) monitoring.

Equipment/procedure	Preferred standards	Variations that should be reported
Electrodes	Describe position of stimulating electrodes: ulnar nerve with negative electrode distal to the positive electrode Describe position of recording electrodes, with active electrode over the muscle belly and indifferent electrode on the insertion of muscle tendon. Hand muscle should be adductor pollicis. Alternative sites can be the first dorsal interosseous or the abductor digiti minimi	Electrode type and size Time from application of electrodes to start of recording (electrode curing time) Monitoring sites other than the ulnar nerve/adductor pollicis muscle, such as the tibial nerve/flexor hallucis brevis muscle at the foot should be specified
Signal quantification	Analog or digitalized EMG signal Gated record of the EMG compound muscle action potential (cMAP) to avoid stimulation artifact	Component of the EMG signal used: area under the curve, amplitude of first negative (upward) deflection, peak-to-peak amplitude, or other specified components of the EMG signal Criteria for acceptance of quality of EMG signal
Amplifier characteristics	Documentation of frequency, range, and common mode rejection rate (signal-to-noise relationship) Continuous recording of signal for storage and documentation Response time of the recorder when analog EMG signal is recorded	The recording should provide an original signal using original data, or the data should be analog-to-digital converted for direct computer analysis

Note: See all standards common to all types of neuromuscular monitoring.

When the mass (the thumb for example) is constant, the acceleration is directly proportional to the force. The acceleration is measured using a small piezo-electric ceramic wafer. The most common site for monitoring acceleration is the adductor pollicis muscle, but other muscles such as the hallucis brevis (foot), orbicularis oculi, and corrugator supercilii (eye) have also been used. However, the responses from these alternative muscles cannot be used interchangeably with the adductor pollicis muscle response and are not recommended for comparative pharmacodynamic studies of new NMBAs.

Because AMG is prone to errors (from artifacts, unstable twitch responses, and movement) more often than MMG and EMG (including those caused inadvertently by the surgeon or other personnel in the operating room), it is advised to secure in place the fingers and the forearm when the thumb is used for AMG monitoring.

Originally, unrestricted movement of the thumb was considered a prerequisite for the use of the method, but there is increasing evidence that a small elastic preload (in the range of 75–150 g) on the thumb may decrease the variability of responses.[47,48] If commercially available preload devices with the same characteristics are used (i.e., IntelliVue NMT Hand-Adapter, Philips, Eindhoven, The Netherlands), the investigator should state the type of preload (and manufacturer) and the resting load (preload in grams or Newtons). If preload is applied by any other means (i.e., a rubber band or a spring) the characteristics of such arrangement should be described. At a minimum, the resting load (grams or Newtons), the change in position during maximum response (cm), and the load at maximum response (grams or Newton) should be stated. If a spring is used, the spring constant (N/m) should be stated. It is important that the preload and its characteristics are maintained during repetitive stimulation.

The AMG method has been compared with the MMG and the EMG methods, and it is well-documented that the methods cannot be used interchangeably.[48–51] The control TOF ratio obtained with AMG is often above 1.0 and higher than the control TOF ratio obtained with MMG. Therefore, to confirm clinically adequate recovery when using AMG, it has been suggested that one should "normalize" the final TOF ratio to the control TOF ratio to improve the accuracy of AMG-derived recovery data (e.g., if control TOF ratio is 1.10, a recovery value of 0.99 corresponds to a 'normalized' TOF ratio of $0.99/1.1 = 0.90$).[52,53] However, more comparative data are needed to determine the impact of this approach. Investigators using AMG should always report the time to an uncorrected (not normalized) TOF ratio of 0.9 and are encouraged to also report the uncorrected times to TOF ratio of 1.0.

Not all commercially available acceleromyographs are suitable for research purposes. For instance, in two of the three acceleromyographs made by Organon (TOF-Watch, TOF-Watch S), a special algorithm was used to calculate the TOF ratio. When the amplitude of T2 is greater than that of T1, the TOF ratio is calculated as T4/T2. Additionally, when the T4/T2 (or the T4/T1) ratio is greater than 1.0 (100%), the TOF-Watch (S) will not display ratios above 1.0 (100%). Although this method of calculating the TOF ratio is probably of little clinical significance,[54] such devices should not be used for research studies. In contrast, the TOF-Watch SX does not have this special algorithm built-in and can, therefore, be used in the research setting. Recently the TOFScan has been recommended for research,[55] since this particular clinically oriented algorithm can be inactivated. Researchers should specify which monitor and software algorithm they are using for their research.

Manufacturers recommendations for setup should be followed and the specific calibration sequence should be described.

Guidelines for monitoring with AMG devices are given in Table 8. See also a section on Standards common to all types of neuromuscular monitoring.

3.3.4 | Kinemyography

The rationale behind kinemyography monitoring of neuromuscular block is the bending of a small piezoelectric sensor positioned between the index finger and the thumb.[56,57] The monitor produces an electric signal that is directly proportional to the movement of the thumb when bending the piezoelectric strip. Only a limited number of studies have compared kinemyography with MMG, and the two methods cannot be used interchangeably.[56,57] This method is not recommended for research purposes.

3.4 | Dose–response studies

The response to varying doses of NMBAs can be determined with high accuracy and precision using current measuring techniques. The quality of any dose–response study relies heavily on such techniques being performed according to the standards described in these guidelines, including the use of appropriate statistical methods. The standards and guidelines outlined in Table 9 refer to the specific design and reporting of such studies.

3.4.1 | Study design

Dose–response investigations during late Phase II and the subsequent stages of clinical trials should be designed as comparative studies. The measured potency of an appropriate reference substance provides an internal control of the quality of the study model and helps to define the relative potency and subsequently the clinically used dosage. Moreover, estimation of relative potencies within the same study should precede clinical studies where it is essential to use equipotent doses.

3.4.2 | Single bolus method

The single bolus method is generally considered as the "gold standard" for measuring the dose–response relationship of NMBAs. It is also a reflection of how these agents are used clinically. Each patient receives only one of the three or more predetermined doses of the drug, after which the degree of maximum block is measured. With a sufficient number of observations, a dose–response curve

TABLE 8 Guidelines for acceleromyographic (AMG) monitoring.

Equipment/procedure	Preferred standards	Variations that should be reported
Electrodes	Describe position of stimulating electrodes: ulnar nerve with negative electrode distal to the positive electrode	Electrode type and size Time from application of electrodes to start of recording (electrode curing time) Monitoring sites other than the ulnar nerve/adductor pollicis muscle, such as the tibial nerve/flexor hallucis brevis muscle at the foot should be specified
Placement of the transducer (piezoelectric accelerometer)	Distal to the interphalangeal joint of the thumb	Alternative sites and position of transducer should be described in detail
Signal quantification	Maximum amplitude of muscle response with free movement of thumb. Align the direction of accelerometer movement along the same axis as thumb movement (less important with tri-axial accelerometers)	Describe whether the accelerometer is uni-directional or three-directional (tri-axial)
Signal stabilization	Immobilization of fingers Transducer firmly fixed to the thumb Pre-tensioning added (thumb adapter) Continuous recording of signal for storage and documentation	Preload and its characteristics should be described in detail

Note: See all standards common to all types of neuromuscular monitoring.

TABLE 9 Guidelines for dose–response studies.

	Preferred standards	Variations that should be reported (and rationale)
General design	Randomization (including method)	Comparison with a reference drug provides relative potencies and a control of validity of the methodology
Single bolus method	At least three different doses Doses should reflect the desired response interval Ideal methods for intermediate- and short-acting agents.	The chosen doses should surround the anticipated ED values but be unlikely to produce frequent 0% and 100% responses
Cumulative method	Acceptable for long-acting agents (a minimum of three doses are recommended)	Acceptable as long as the dose increments are given within a brief period (relative to the duration of action of the drug)
Method of stimulation	Single twitch (ST) at 0.1 Hz	TOF pattern of stimulation
Linearizing transformations	Log values of doses Probit, logit, or arcsine values of percentage responses are recommended	The convention of using probit or logit responses facilitates communication of (slope) data
Handling of 0% and 100% responses	These undefined probit or logit values should be adjusted by half the assumed resolution of the measuring method	For instance, if the measurements can discriminate a 2% difference in response, ≈ 100% should be adjusted to 99%, and ≈ 0% should be adjusted to 1%
Reporting (presentation) of data	ED_{50} recommended Slope (unit) to be described Scatterplot of individual observations and a composite dose–response curve Confidence intervals for values	ED_{50} is usually a robust measure ED_{50} can be influenced by the choice of transformation and the existence of 100% responses

can be constructed using regression analysis. A drawback of this method is the requirement of a larger sample compared to the cumulative dose method. Although this approach using only one or two bolus doses has been described,[58,59] it is recommended to use a minimum of three doses as this remains the most validated method.

3.4.3 | Cumulative dose method

The cumulative method requires fewer patients and individual dose–response curves are constructed for each subject. In this method, all the increments of the drug are given to the same patient, the next dose being given when the previous dose has produced an approximately stable response. This method is validated for long-acting agents if the increments are given within a brief period.[60] The conventional technique of administering the cumulative doses is to achieve approximately 95% block in all patients. This may, however, produce bias by requiring a larger number of increments in poor responders, reducing further the measured response values as a result of the longer time for drug disposition. This method will probably have less use in the future because the development of new long-acting NMBAs is unlikely.

The method of stimulation also influences the apparent potency as determined by dose–response studies, with the TOF method producing an apparently higher potency (lower absolute ED_{50} and ED_{95} values).[17,18] Ideally, the ST method should be used for potency determination in the same way as for determining the time to onset of maximum block.

See the section on Statistics for data management and statistical considerations.

3.5 | Monitoring onset and time course of neuromuscular block

Neuromuscular block can be divided into different periods, each period being associated with its own characteristics and time course profile. These periods are onset of block, periods of complete, deep, and moderate neuromuscular block, and the recovery period (Figure 2). The terminology and methods used when measuring the various periods of neuromuscular block are described below.

3.5.1 | Onset of neuromuscular block

Nerve stimulation patterns and the time interval between stimuli affect the onset time and subsequent time course variables in such a way that stimulation patterns cannot be used interchangeably. Consequently, results obtained with one pattern of nerve stimulation cannot necessarily be compared with results obtained using another pattern. Onset time is determined using 0.1 Hz ST stimulation or TOF stimulation (2 Hz for 1.5 s every 15–20 s). The time interval between stimulations should not be less than every 10 s[61] for ST or every 15–20 s for TOF.[19]

3.5.2 | Dose of NMBA

Clinically, the onset time is usually defined as 2 or more times the estimated effective dose (ED), reflecting the doses that are often used for tracheal intubation. Administration of these larger doses shortens the time to 100% neuromuscular block and is required during a rapid sequence induction and intubation. It should be noted that with administration of these large doses, the time until 100% twitch depression does not relate to true maximum block, which occurs at maximum receptor occupancy at the neuromuscular junction.[62,63] As this cannot be measured, the onset time profile (i.e., speed of action) of an NMBA is best assessed using a subparalyzing dose, that is, a dose that produces less than 95% twitch depression during either 0.1 Hz or TOF stimulation It should be specified if the dose of the NMBA is calculated on parameters other than ABW.

3.5.3 | Start- and end-points

The start- and end-points of onset time should be assessed at a measurable twitch response. While the start point for measurement of onset is at the beginning of administration of the NMBA, the endpoint should not be considered when the ST response disappears, that is, at 100% twitch depression (see above). Onset time should be measured

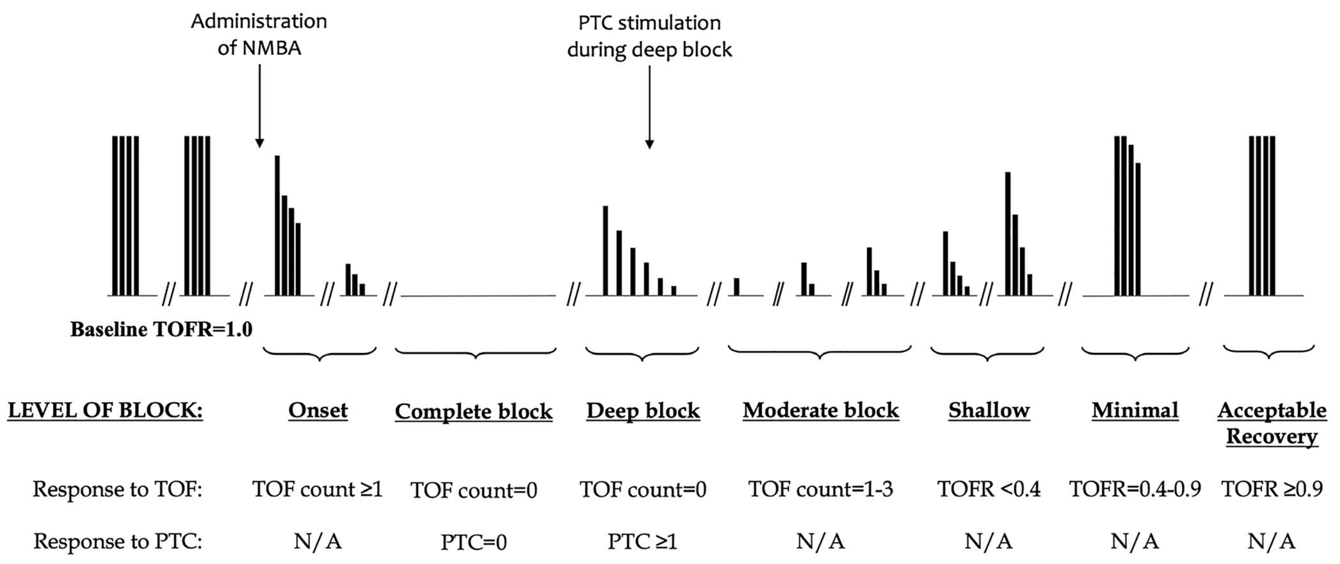

FIGURE 2 Levels of block after a normal intubating dose of a non-depolarizing NMBA, as classified using PTC and TOF stimulation.

as the time from drug administration until 95% twitch depression of any dose producing more than 95% twitch depression. For subparalyzing doses (doses producing less than 95% ST depression), the end-point (maximal effect) should be defined as the first of three consecutive twitch responses with the same or increasing amplitude.

The onset times of different NMBAs should be compared using subparalyzing doses.

3.5.4 | Duration of drug injection

A short duration of drug injection is important in order to avoid any influence on onset time of the speed of injection per second. For the sake of consistency, 5 s should be used as the injection time for an initial or repeat bolus dose. Deviation from this should be specifically stated and the reason for the deviation should be explained. The injection should be followed by a 20-mL saline flush over 5 s while maintaining the patient's arm elevated vertically.[64]

3.5.5 | Definition of onset

This is defined as the time period from the start of injection of the NMBA until 95% suppression of T1 or ST in case of complete disappearance of responses, or to the degree of maximum suppression of these responses when the block is less than complete.

3.5.6 | Definition of depth of neuromuscular block

1. Period of **complete** block is defined as the time period when there is no response to PTC stimulation (and no response to TOF stimulation).
2. Period of **deep** neuromuscular block is defined as the time period with no response to TOF stimulation but a response to PTC.
3. Period of **moderate** neuromuscular block starts with the reappearance of T1 (TOFC = 1) and ends with the reappearance of T3 (TOFC = 3).
4. Recovery period is defined as the time period from the reappearance of T4 (TOFC = 4) until the recovery of TOF ratio to control values. Depending on the TOF ratio, the recovery period is divided into the period of **shallow** block (TOF ratio ≤0.4) followed by the period of **minimal** block (TOF ratio >0.4 but <0.9). A TOF ratio ≥0.9 is considered **acceptable recovery**. If another end-point of recovery is used, it should be identified (Table 10).

3.5.7 | Definition of Duration 25% and Duration TOF ratio 0.9

Duration 25% (Dur 25%) is the time from the start of injection of NMBA until T1 (or ST) has recovered to 25% of the control (baseline) value. Duration TOF 0.9 (Dur TOF 0.9) is defined as the time from start of injection of the NMBA until recovery of the TOF ratio to 0.9. Irrespective of the monitoring technique used (MMG, EMG, or normalized AMG), the endpoint for the Dur 25% should be considered as the time at which the first of three consecutive responses (T1 or ST) has recovered to a value that is 25% of control. Similarly, the endpoint for the Dur TOF ratio 0.9 should be considered as the time at which the first of three consecutive TOF readings reach a TOF ratio >0.9.

3.6 | Reporting of surgical conditions data

Several studies assessed the impact of the depth of neuromuscular block on surgical conditions and complications. Studies investigating the effect of different levels of NMB should report how the level of intraoperative neuromuscular block is maintained (e.g., infusion or bolus administrations), and they should maintain a clear gap between levels of block (i.e., TOFC >2 for moderate block and a PTC 1–3 for deep block). Depending on the monitor technology used, the number of delivered post-tetanic twitches may vary from 10 to 20. Thus, to characterize a deep block both, the number of detectable PTC responses and the number of delivered post-tetanic twitches should be reported (e.g., 6/10 PTCs). For authors investigating the effect of the level of NMB on the quality of surgical conditions, it is recommended to employ a validated surgical rating scale to report results in a standardized manner.[66]

Along with the surgical rating scale data, authors are encouraged to report the occurrence of surgical and/or anesthetic complications (e.g., bleeding or perforation of organs) by using the

TABLE 10 Definitions of the depth of neuromuscular bock.

Depth of block	Post-tetanic count	Train-of-four count	Measured train-of-four ratio
Complete block	0	0	0
Deep block	≥1	0	0
Moderate block	N/A	1–3	0
Shallow block	N/A	4	≤0.4
Minimal block	N/A	4	>0.4 but <0.90
Acceptable recovery	N/A	4	≥0.90–1.0

Note: From Brull and Kopman.[65]
Abbreviation: N/A—Not applicable.

Clavien–Dindo scale for classification of surgical complications[67] or a similar scale.[68]

3.7 | Reporting of NMB antagonism

Reversal of block is measured from a defined degree of recovery, for example, deep block (PTC ≤3, TOFC = 0), or from 25% recovery of the twitch response (ST or T1) during either 0.1 Hz or TOF stimulation, or in clinical studies from the return of the first (T1), second (T2), third (T3) or fourth (T4) twitch in the TOF response, or from specific TOF ratios, until a TOF ratio ≥0.9 is reached. The degree of recovery present at the time of reversal should be recorded and described. Moreover, the type and dose of the antagonist should be described, and it should be specified whether the dose was calculated based on ABW or other dosing schedule. Just as for the NMBA, the reversal agent is administered intravenously over 5 s, followed by a 20 mL saline flush over 5 s (Table 2). Stability of recovery should be observed for at least 10 min after having reached the threshold (TOFR ≥0.90) and reported. The main anesthetic (volatile vs. intravenous agents) administered during recovery and the respective end-tidal concentration or estimated effect-site concentration throughout recovery of neuromuscular function should be reported.

3.8 | Reporting of tracheal intubation, airway and respiration, and pulmonary complications

The neuromuscular junction of respiratory muscles is a primary target for all NMBAs. Therefore, clinical studies involving neuromuscular pharmacology and monitoring of the respiratory system should include clinically relevant details pertaining to this system. The following recommendations will consider outcome parameters related to bag-mask ventilation, intubating conditions, airway physiology and function, and postoperative pulmonary complications.

3.8.1 | Bag-mask ventilation

As the ease with which bag-mask ventilation can be provided may differ as a function of the individual clinician's expertise and the NMBA and its pharmacologic properties, it is suggested that this parameter be evaluated based on a validated and established scoring system. In an elective situation, such evaluation of bag-mask ventilation can be done using a standardized evaluation scale[69,70] (see Tables 11, 12).

3.8.2 | Intubating conditions

While evaluation of intubating conditions is essentially subjective and based on the skill of the individual performing the intubation, the use of scoring systems allows some standardization of assessments. Simplified qualitative intubation scoring systems should be used for such assessments without assigning numerical values to any of the variables. Statistical analysis appropriate for ordinal scales should ideally be used to analyze intubation condition scores.

Interpretation of intubating conditions is critically dependent on prior airway assessment. To be able to make comparisons of intubation conditions between patient groups, an initial anatomical airway assessment must therefore be performed and reported. The evaluation of the patient correlates the predicted difficulty with that observed. Baseline characteristics should typically include Mallampati or Modified Mallampati score,[71] thyromental distance,[71] mouth opening test,[71] upper lip bite test,[72,73] and BMI.[74] Since none of the commonly described bedside screening tests have sufficient diagnostic accuracy, reporting of multiple airway evaluation measures is encouraged.[71,75]

Ease of laryngoscopy should be evaluated as a separate entity from ease of intubation.

The following factors that are presented in detail in Table 13 should be described for a comprehensive qualitative evaluation of intubating conditions:

1. Ease of laryngoscopy
2. View of vocal cords
3. Position and/or movement of vocal cords in response to tracheal tube insertion

It must be defined if direct laryngoscopy, videolaryngoscopy, or fiberoptic bronchoscopy was used, the number of attempts, the duration of attempted intubation, the number of assistants available, whether the tracheal intubation was ultimately successful, and whether several different intubation devices were used.

Standard intubating doses of rocuronium (or succinylcholine) should be used as the standard NMBA in comparative studies of rapid sequence induction and the assessor should be blinded for assessment of intubating conditions.

As the depth of anesthesia at the time of tracheal intubation influences the intubating conditions, the anesthetic depth should be standardized and described, although not necessarily objectively measured. Ideally, the anesthesia technique should be identical between groups in comparative studies of NMBAs. It is considered acceptable to use opioids in moderate doses in studies assessing intubating conditions with differing NMBAs, but the dose should be such as to allow discrimination of the effects of NMBA. In addition, the same dose of opioids, preferably based on BW, should be administered to all groups in comparative studies. It is recognized that the depth of anesthesia may be lighter during rapid sequence induction of anesthesia, which will influence comparisons of intubation conditions in a rapid sequence of induction with standard induction techniques.

The time sequence of laryngoscopy and intubation should be clearly recorded. For example, when intubation is planned to be carried out at 60 s, laryngoscopy may be started 50 s after drug administration and intubation carried out at 60 s, the intubating procedure being completed after another 20 s.

TABLE 11 Initial mask ventilation classification and description.

Classification	Description/definition	No. of selections	% of cases
Grade 0	Did not attempt	272	17.7
Grade 1	Easy mask	1079	70.4
Grade 2	Difficult mask requiring an oral airway or other adjuvant	128	8.3
Grade 3	Very difficult mask ventilation requires two practitioners	22	1.4
Grade 4	Unable to mask ventilate	2	0.1
Comments		22	1.4
Total		1533	

Note: From: Han et al.[69]

TABLE 12 Final mask ventilation classification and description.

Classification	Description/definition	No. of selections	% of cases
Grade 0	Ventilation by mask not attempted	449	24.2
Grade 1	Ventilated by mask	1010	54.4
Grade 2	Ventilated by mask plus oral airway or other adjuvant	366	20.0
Grade 3	Difficult mask ventilation (inadequate, unstable, or requiring two practitioners)	22	1.2
Grade 4	Unable to mask ventilate	1	0.05
Comments		6	0.3
Total		1854	

Note: From: Han et al.[69]

TABLE 13 Evaluation of intubating conditions.[a]

Variable assessed		Clinically acceptable	Not clinically acceptable
	Excellent	Good	Poor
Laryngoscopy[b]	Easy	Fair	Difficult
Vocal cords position	Abducted	Intermediate/moving	Closed
Reaction to insertion of the	None	Slight[c]	Vigorous/sustained[d]
tracheal tube and cuff inflation			
(Diaphragmatic movement/coughing)			

Note: From: Viby-Mogensen et al.[1]
[a]Intubation conditions (Excellent: all qualities are excellent; Good: all qualities are either excellent or good; Poor: the presence of a single quality listed under "poor").
[b]Laryngoscopy (Easy: jaw relaxed, no resistance to blade insertion; Fair: jaw not fully relaxed, slight resistance to blade insertion; Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy).
[c]One to two weak contractions or movement for less than 5 s.
[d]More than two contractions and/or movement for longer than 5 s.

Time events should be reported in relation to the start of the injection of the NMBA. When the drug is administered over a different time period, this should be clearly stated and explained. If the tracheal intubating conditions are being assessed at different time intervals after a single investigational product to find the most suitable time for intubation, the conditions in a particular patient should be assessed only once at a predetermined time.

There are studies assessing intubating conditions without the use of NMBA.[76] However, in many of these studies, the intubating conditions have not been assessed using a standard scoring system. Consequently, the use of different scoring systems makes it difficult to compare conditions from different studies. While it is most relevant to study intubating conditions without using NMBAs, it is recommended that the method of assessment and time at which the intubating conditions are assessed follow these guidelines. It is also desirable to have a control group receiving an NMBA in such studies.

Intubating condition studies should ideally contain outcome measures of relevance for post-intubation adverse events, such as postoperative hoarseness.[77] It is also considered part of good practice to standardize measurement of cardiovascular responses (heart rate, blood pressure, and oxygen saturation) at a specified time (2 min) after tracheal intubation.

In general, clinicians do not routinely monitor the muscle groups of interest during intubation (i.e., the diaphragm and/or vocal cord muscles). Nonetheless, researchers should specify which muscle group is being monitored to determine onset of neuromuscular block and subsequent time of intubation. The adductor pollicis muscle is commonly monitored following ulnar nerve stimulation as it is convenient and the best-documented nerve-muscle unit for monitoring neuromuscular block; the degree of block in this muscle correlates poorly with the temporal development of neuromuscular block in muscles of relevance for intubation, for example, laryngeal muscle groups. Another muscle that can be used to better follow the temporal development of neuromuscular block in the upper airways is the corrugator supercilii.[78]

It is suggested to assess intubating conditions as a separate variable from objective monitoring of neuromuscular block depth.

3.8.3 | Postoperative airway function

Residual effects of NMBAs can impair vital airway functions such as upper airway patency,[79,80] impair swallowing[81,82] and also cause a reduction in the hypoxic ventilatory response.[83,84] Upper airway obstruction can be measured clinically (e.g., visual observation, cessation of airflow, polysomnography), anatomically (e.g., computed tomography, magnetic resonance imaging), or functionally in an experimental setting (e.g., peak inspiratory flow, critical closing pressure, and pharyngeal critical closing pressure). Studies on pharyngeal function and control of breathing that require technically advanced settings, includingstate-of-the-art imaging or respiratory gas and airway flowmetry, are not included in these guidelines.

If arterial hypoxemia is an outcome parameter, the level of oxygen saturation should be defined as well as the duration of hypoxia, as a measure of hypoxic load. In this context, addition of supplemental oxygen must be stated, including flow rate, administration route, and timing and duration of administration within the perioperative course. The same considerations are of importance for the need of airway manipulation devices or support. The type of airway should be reported. In clinical studies, reintubation after tracheal extubation should be noted along with the indication for reintubation.

3.8.4 | Postoperative pulmonary complications

Studies focusing on the effect NMBAs on postoperative pulmonary complications should include information concerning pre-existing comorbidities (i.e., basic demographics), surgical procedure details, intraoperative ventilator settings, and postoperative respiratory management, such as usage of noninvasive ventilatory (NIV) support, high-flow oxygen device, and oxygen concentration delivered.

Most importantly, a defined standardized outcome parameter for postoperative pulmonary complications must be used and chosen based on previous studies in relation to the specific study. During the last decade, there has been a focus on postoperative pulmonary complications in general and several large perioperative outcome studies (e.g., PERISCOPE, POPULAR, STRONGER) have been launched[85,86]; see also ESA Clinical Trial Network (https://www.esahq.org/research/clinical-trial-network/). Importantly, Standardized Endpoints for Perioperative Medicine (StEP) have described detailed definitions of postoperative pulmonary complications.[87] These standardized definitions are based on mechanism and also include a severity scale in order to make the grading of postoperative pulmonary complications more objective (Table 14). The StEP group also defined postoperative pneumonia and postoperative respiratory failure.[87] It is recommended that these consensus guidelines on postoperative pulmonary and respiratory complications be adopted in outcome studies on NMBA and neuromuscular monitoring.

For comparisons between studies, researchers should strive to standardize intraoperative ventilatory settings such as ventilatory

TABLE 14 Recommended definition of postoperative pulmonary complications.

Postoperative pulmonary complications
Mechanism
Composite of respiratory diagnoses that share common pathophysiological mechanisms including pulmonary collapse and airway contamination:
i. Atelectasis detected on computed tomography or chest radiograph.
ii. Pneumonia using US Centers for Disease Control (CDC) criteria.
iii. Acute Respiratory Distress Syndrome using Berlin consensus definition.
iv. Pulmonary aspiration (clear clinical history AND radiological evidence).
Severity
None: planned use of supplemental oxygen or mechanical respiratory support as part of routine care, but not in response to a complication or deteriorating physiology. Therapies that are purely preventive or prophylactic for example high-flow nasal oxygen or continuous positive airways pressure (CPAP) should be recorded as none
Mild: therapeutic supplemental oxygen <0.6 FiO_2
Moderate: therapeutic supplemental oxygen ≥0.6 FiO_2, requirement for high-flow nasal oxygen, or both
Severe: unplanned noninvasive mechanical ventilation, CPAP, or invasive mechanical ventilation requiring tracheal intubation
Exclusions
Other diagnoses that do not share a common biological mechanism are best evaluated separately and only when clearly relevant to the treatment under investigation:
i. Pulmonary embolism
ii. Pleural effusion
iii. Cardiogenic pulmonary edema
iv. Pneumothorax
v. Bronchospasm

mode, pressures, tidal volumes (expressed in mL/kg), oxygen fraction, and PEEP. Postoperatively, the immediate patient location should be reported (e.g., postoperative care unit, intensive care unit (ICU), regular ward, etc.) as well as the need for supplemental oxygen or need for ventilatory support such as noninvasive ventilation (NIV), high-flow oxygen, or tracheal intubation and mechanical ventilation, etc.

The temporal pattern of the postoperative pulmonary complications reported must be defined, such as hours, days, or weeks postoperatively.

3.9 | Special patient populations

3.9.1 | Intensive care unit patients

NMBAs may be useful in the ICU for several variably defined indications. Other than for emergent intubation, NMBAs are generally reserved for those in need of mechanical ventilation in whom conventional strategies of sedation and analgesia have failed. The NMBA duration of action varies from patient to patient, particularly during long-term administration, and, despite the increasing use of invasive monitoring in many aspects of intensive care, routine monitoring of neuromuscular transmission in ICU patients is not common.[88] Literature on best practices to standardize research in neuromuscular pharmacology and monitoring in the ICU settings is very limited. For this reason, investigations of outcomes in critically ill patients are difficult to compare.

Clinical factors and confounders that contribute to heterogeneity of information in the critical setting include multiple rationales and indications for use of NMBAs in ICU patients, such as short-term (single dose) use of NMBA (for tracheal intubation, minor short procedures, etc.); acute respiratory distress syndrome or acute lung injury; profound hypoxemia, respiratory acidosis, or hemodynamic compromise; increased intracranial pressure or intra-abdominal pressure; therapeutic hypothermia after cardiac arrest; lung-protective ventilation; prone positioning ventilation; and tetanus.

Furthermore, ICU patients may have multi-organ system involvement, with various effects on PK/PD of most NMBAs and antagonists. Multiple drugs and infusions are frequently co-administered, and many may affect the PK/PD of NMBAs and antagonists (antibiotics, calcium, magnesium, etc.). ICU patients also may develop tissue edema, impacting monitoring of depth of block, since tissue edema decreases the effectiveness of neurostimulation.[89] Longer-term use of NMBAs may lead to development of critical illness myopathy and/or polyneuropathy[90,91] with various effects on neuromuscular transmission and monitoring. Finally, due to prolonged infusions or in traumatic brain injury patients, NMBAs may cross the blood–brain barrier and produce central anti-cholinergic effects.

Recommendations

1. Clearly indicate the patient's main diagnosis and all secondary illnesses that are likely to affect PK/PD of NMBAs, antagonists, and neuromuscular monitoring.
2. Clearly indicate the patient temperature (important for cisatracurium metabolism), hydration status (presence of edema), concurrent medications affecting NMBAs and antagonists, such as the potentiating effects of corticosteroids and aminoglycosides on muscle dysfunction.[92]
3. Describe the use of vasoactive drugs in the critically ill patient as they may cause changes in skin resistance that impair the accuracy of neuromuscular monitoring measurements.
4. Clearly describe the total NMBA dose (administered by separate boluses and/or by continuous infusions), as well as the infusion duration; there is a significant relationship between infusions for longer than 48 h, drug and metabolite accumulation, and development of prolonged weakness.[92]
5. Specify how NMBA effects are monitored: subjectively (qualitatively) by tactile or visual means using a peripheral nerve stimulator, or objectively (quantitatively) using a neuromuscular monitor.
6. If quantitative assessment is used, specify the monitoring technique: AMG, electromyography, kinemyography, MMG, etc.
7. Indicate whether the quantitative monitor was calibrated (specify the calibration characteristics and sequence) and whether the results were normalized to baseline (for AMG).
8. Specify the neurostimulation current intensity (in mA), the stimulus pulse duration (in msec), the stimulating pattern [TOF; double burst stimulation; ST; TOF count, or PTC], and the frequency of testing (e.g., every 20 s, every 1 min, etc.)
9. Specify the muscle monitoring site (peripheral: adductor pollicis, first dorsal interosseous, or abductor digiti minimi muscles vs. central: corrugator supercilii muscles).
10. Report technical problems related to the operation of the monitoring device, such as interference with skin electrode placement, loss of skin adhesion, and suboptimal delivery of the desired current.

3.9.2 | Pediatric patients

The pediatric anesthesia literature is severely limited with respect to standardized guidelines for neuromuscular monitoring of pediatric patients. In view of the literature suggesting better airway management outcomes in pediatric patients intubated with the use of NMBA,[93] good clinical pediatric research practice guidelines are essential to better care for infants and children of all ages. A number of factors contribute to the paucity of pediatric neuromuscular management data. The developmental changes in the neuromuscular junction physiology limit the comparison of responses to standardized stimuli.[94] Premature newborns, neonates, and infants less than 2 months of age lack muscle strength and have lower acetylcholine stores. In this population there is a significant fade with increasing stimulation rates from 20 to 50 to 100 Hz, and post-tetanic facilitation does not incrementally increase with an increase in frequency,[94] and a 5 s, 100 Hz tetanic stimulation generally leads to post-tetanic exhaustion. The majority of the pediatric pharmacokinetic and pharmacodynamic studies performed before mid-1990s were conducted using either MMG (Grass FT-03 or Grass FT-10 force–displacement transducer, Grass Instrument Co.) or electromyography (Relaxograph, Datex, Helsinki, Finland). Although MMG is still considered the research standard for neuromuscular monitoring, recent evidence demonstrates that EMG correlates well with MMG, is reliable and reproducible, and is easier to use in clinical research.[40,95] Mechanomyographs are no longer manufactured for clinical use, but reference MMG-based monitors are used for validation of newer EMG-based monitors.[40] AMG (TOF-Watch SX, Organon, Cork, Ireland) has been used in pediatric studies. Similar limitations of AMG use in pediatric patients as in the adult population exist, including over-estimation of TOF ratio (inverse fade) when compared with MMG and EMG[96] and the "staircase" phenomenon associated with ST stimulation.[97] AMG monitors also require a significant amount of time (5–10 min) for stabilization of the baseline signal, although a 5 s tetanic stimulation may prevent the staircase phenomenon and shorten the signal stabilization requirement.[98] Neonates and young infants might require a manual increase in the gain of the transducer in order to obtain a first twitch in the TOF sequence (T1) equal to 100%.[99] Recent reports describe the successful use of EMG in pediatric patients.[41] There currently are no studies that have determined the supramaximal current requirements as a function of age, but in pediatric patients weighing 20–60 kg, the current intensity at a pulse width of 0.2 ms was 30 mA in 3%; 40 mA in 42%; 50 mA in 28%; and 60 mA in 22% of patients, while the average baseline amplitude of the response was 7.5 mV.[41] Minimum current amplitudes necessary for visual detection of contractions are around 20 mA (with a range of 10–45 mA), similar to those in adults.[100] The small size of the pediatric patients imposes technical challenges regarding appropriate equipment. Lead placement and electrode size may affect current density and therefore the required charge for a supramaximal response. Temperature changes affect the EMG electrical signal amplitude to a lesser extent than MMG or AMG,[43] but since neonates are particularly prone to intraoperative hypothermia, this may affect the evoked responses.

Recommendations:

1. In pediatric patients the BMI should be adjusted for age and sex. Such a BMI calculator is available at https://www.cdc.gov/healthyweight/bmi/calculator.html (Center for Disease Control and Prevention). The patients should be categorized as:

- Underweight: <5th percentile,
- Normal or healthy weight: 5th to 85th percentile,
- Overweight: 85th to 95th percentile
- Obese: ≥95th percentile

2. Age groups classification:
- premature—birth before the start of 37th gestational week
- neonate—0 to <1 month
- infant—1 month to 1 year
- children—2–11 years
- teenager—12–17 years

3. Use silver/silver chloride (Ag/AgCl) pediatric-sized nerve stimulating electrodes. The negative electrode should always be distal to the positive electrode.[14] An alternative position is to place the positive electrode on the ulnar groove at the elbow in order to improve ulnar nerve depolarization.
4. Temperature should be maintained constant; central temperature above 35°C and peripheral temperature at the monitored muscle above 32°C.
5. For any meaningful comparison between technologies (AMG, EMG, and MMG), the AMG monitor must be calibrated. For AMG, final recovery TOF ratios must be normalized to the baseline ratio, unless a tetanic pre-stimulation is performed.[98]
6. Application of a 5-s 50-Hz tetanic stimulation prior to calibration may prevent the staircase phenomenon and shorten the signal stabilization period.[98]
7. A preload can be considered for neonates and infants, but a clear description of technique needs to be presented.
8. Recent reports describe the successful use of EMG in pediatric patients.[41]

3.9.3 | Patients with neuromuscular disease

Research data on physiology and pharmacology of neuromuscular transmission in patients with neuromuscular disease are rare and often difficult to compare. Although neuromuscular monitoring follows basically the same guidelines and rules in the perioperative setting and in patients with neuromuscular disease, some specific factors must be considered in the later patient's population to obtain valuable and reproducible data. Depending on the underlying neuromuscular disorder, monitoring site and monitoring technology as well as stimulation parameters and stimulation pattern may contribute to deviation of the data.

The following suggestions apply to studies performed in patients with central motor neuron lesions:

1. Bilateral lesions: This may influence resistance to non-depolarizing NMBAs at different extremities, depending on the location and the distribution of central lesion. In paraplegic patients, there is a clear difference between the affected lower and non-affected upper body in terms of sensitivity. Typically, the non-affected upper body is used for neuromuscular monitoring. The monitoring site should be described. Because of alterations of the electromechanical coupling, the performance of EMG monitoring on the paretic part of the body is limited.
2. Unilateral lesions (hemiparesis/hemiplegia): There is a clear resistance to non-depolarizing NMBAs on the paretic, compared to the non-paretic, side (note: slight resistance to non-depolarizing NMBAs may also develop on the non-affected side). The non-paretic side is preferred for neuromuscular monitoring. The monitoring site should be described. Because of alterations of the electromechanical coupling, the performance of EMG monitoring on the paretic site is limited.

3. Amyotrophic lateral sclerosis: The return of TOFR to 0.9 may precede the return of the baseline twitch (T1) height to baseline.
4. Guillain-Barre's syndrome: Because of the ascending nature of the disease neuromuscular monitoring usually can be performed at the upper extremities. The monitoring site should be described.
5. Charcot–Marie-tooth disease: Upper extremities are preferable for monitoring because lower extremities are usually more affected. The monitoring site should be described.

In patients with presynaptic neuromuscular junction abnormalities (Lambert-Eaton myasthenic syndrome), both ST and TOF stimulations are unreliable, because T1 amplitude is usually small and high variability exists in TOF ratio even before administration of the NMBA. After tetanic stimulation, post-tetanic facilitation occurs resulting in an increase of up to 16-fold in twitch height. In patients with postsynaptic abnormalities (myasthenia gravis), the n-AChRs are downregulated, leading to resistance to agonists (depolarizing NMBA) and increased sensitivity to antagonists (non-depolarizing NMBA), resulting in TOF ratios <1.0 (neuromuscular fade) at baseline, even prior to NMBA administration.[101]

4 | RESEARCH, METHODOLOGICAL AND STATISTICAL CONSIDERATIONS

Statistics is the discipline concerned with the presentation treatment and analysis of numerical data. Research methodology, whilst incorporating statistical analyses, also includes all the stages and processes involved in conducting research. This usually starts with a research question or hypothesis. It is then logical to summarize the information about the topic, already available, usually in the form of a *systematic review* with *meta-analysis*, if appropriate. Appropriate ethical review and approvals will be required. Applications to funding and grant awarding bodies are submitted as appropriate, and the study or clinical trial should be registered in an internationally recognized trial registry prior to enrolling patients or subjects. Evidence of favorable ethical review and trial registration are now considered as essential by the mainstream scientific publishing journals.

4.1 | Sample size calculations

From a statistical and study design perspective the first step is the sample size calculation. Especially for early trials, this defines the minimum clinically important difference (MCID) or effect size and clearly identifies the primary outcome variable or measure.[102] There are four parameters that need to be considered for a continuous variable, which can be condensed to three if an effect size or standardized difference is used.

1. Size of the MCID or effect size.
2. Variability or distribution of data, usually represented by the standard deviation (SD)
3. Probability of detecting a true positive result (power $1 - ß$), ≥ 0.80 is typical.
4. Probability of detecting a false positive result (α error), a two-sided alpha level of 0.05 is typical.

As mentioned, the MCID is the most important and helpful aspect. An estimate of the variability or SD can often be obtained from previously published research or from some pilot data. Even in the absence of prior data, it is still possible to make certain assumptions and either simulate the data or estimate an empirical sample size calculation using for example the *one-fifth rule*. First, we estimate what is the likely range of values that may exist for the variable in question. A simple example could be a clinically relevant guesstimate of a range from the minimum to maximum duration of neuromuscular block in a particular setting. We know from the Gaussian distribution that 99% of the range of values is contained within six SDs or *six-sigma*. We divide the range of values by six we get a simple estimate of the SD. In practice to get a more conservative estimate for the SD, it is usual to divide by five, hence the *one-fifth rule*.

As suggested above, the first two parameters can be combined as the *standardized difference*. This is the MCID divided by the SD for continuous data or the difference in proportions divided by the SD in proportions for categorical variables:

$$\text{Standardized difference for continuous data} = \frac{\text{MCID}}{\text{SD}},$$

$$\text{Standardized difference for proportions} = \frac{p_1 - p_2}{\sqrt{p(1-p)}}.$$

Type I error is the risk of a false positive result, also termed alpha (α) error. It refers to the situation where $p < .05$ and causes the null hypothesis to be incorrectly rejected when it should have been accepted.

Type II error is the risk of a false negative result, also termed beta (ß) error. It refers to the situation where $p > .05$ and the null hypothesis is accepted incorrectly. Power $(1 - ß)$ is the probability of detecting a true positive result. Researchers usually consider a study to be adequately powered if it has a power of 0.80 or greater.

4.2 | Statistical hypotheses

4.2.1 | Inequality

The usual hypothesis that is tested is that of *inequality*, (two-sided), often incorrectly termed *superiority*, which is actually a one-sided test. For inequality, the *null hypothesis* (H_0) of no difference or effect is tested and evidence is then accrued to accept or reject this in favor of the *alternative hypothesis* (H_A) of inequality in that there is a difference or effect. A *p-value* represents the probability that the observed difference, effect size, occurred assuming the null hypothesis is true.

Conventionally, $p < .05$ (*two-sided*) is considered significant. The use of *one-sided p-values* should be avoided, are rarely appropriate, and if used, its rationale must be clearly explained and justified.[103] Any difference or effect size should also be presented, usually with a 95% confidence interval.

When *multiple comparisons* or hypotheses are tested, usually involving three or more groups or treatments, the risks of a type I error and false positive findings are increased.[104] The total possible number of comparisons is:

$$(k(k-1))/2,$$

where k is the number of groups or treatments. In this situation, the threshold p-value for significance should be lowered to keep the overall type I error rate at <0.05 for all tests. Various techniques to adjust for multiple comparisons are available, the simplest, though conservative, is the *Bonferroni correction*. Here, the p-value that is obtained is simply multiplied by the number of comparisons, or, more logically, the type I error value of <0.05 is divided by the number of comparisons to establish a lower threshold p-value at which to conclude significance. Similar corrections should be used to widen the 95% CI for differences and effects.The best research practice is to try and avoid multiple hypotheses and to define a primary research outcome with additional appropriate secondary aims.

4.2.2 | Equivalence and non-inferiority

Often a new treatment or intervention is introduced that may have benefits in terms of adverse effects or cost. Here the interest of the researcher is to show that the treatments are equivalent, or at worst, non-inferior, to the reference or standard in clinical use. Non-inferiority trials can be considered as a one-sided case of equivalence.[105] The hypotheses to be tested then follow as:

H_0: Inequality or inferiority.
H_A: Equivalence or non-inferiority.

The important distinction for these analyses is that equivalence or non-inferiority margins (δ) must be defined at the outset. Typically, equivalence is accepted when the mean of the new intervention being tested, (μ_T) is not lower than 80% or higher than 120% of reference (μ_R). The equivalence interval [δ_1, δ_2], where δ_1 and δ_2 represent -20% and $+20\%$ of μ_R, respectively

$$H_0 : \mu_T - \mu_R \leq \delta_1 \, or \, \mu_T - \mu_R \delta_2.$$

In testing H_0, both sides are tested separately using the two-one-sided test (TOST) procedure. Both need to be rejected individually to reject the null hypothesis altogether and then accept the H_A of equivalence. For non-inferiority, we are then only interested in the lower one-sided margin or test.

An alternative and more intuitive approach is to use the ratio μ_T/μ_R and accept equivalence if the 90% CI for this ratio is wholly contained within the 0.80 and 1.25 margins. The 90%CI follows from the TOST at $p < .05$ for both sides. Likewise, for non-inferiority, we are only interested in the lower one-sided margin.

The interpretation of the results of non-inferiority trials should be evaluated carefully, with consideration given to the choice of the comparator, the size of the margin ($-\delta$), and presence of bias.

4.3 | Agreement and repeatability

For new technologies and measurement modalities, assessments of repeatability precision, and agreement are required. Generally, correlation methods only test for an underlying linear trend in the measures, not the precision, although intraclass correlation and Lin concordance coefficients may be useful. A useful approach to assess agreement is to plot the differences between the two methods against the average across the range of clinically relevant values. The Bland–Altman plot then allows the bias and the 95% limits of agreement (± 2 SD bias) to be plotted.[106] The bias and limits should be presented with 95% CI. The plots should be inspected for heteroscedasticity such as increasing scatter with magnitude or proportionality. Transformations, such as logarithmic, may be required. When repeated measures in subjects are performed then appropriate corrections to the 95% limits of agreement to account for within- and between-subject variabilities are required.

An important consideration is to decide a priori the clinically acceptable discrepancy.[107] A practical approach is to define a tolerability interval that separates measurements that could cause extreme or opposing interventions and assess the potential for extreme-to-extreme misclassification. The strength of agreement is then defined as the agreement interval expressed as a proportion of the predefined tolerability interval (Table 15).

4.4 | Dose–response studies

In dose–response studies, patients are randomized in three or more groups to different doses to characterize the dose–response relationship. Probit and logistic regressions with maximum likelihood estimation can be used to linearize the ED or effective concentration (EC) in a percentage of subjects between ED_{16} to ED_{84} and produce estimates for the asymptotic extreme lower- and upper-point estimates, such as ED_{95} with 95% CI. For the simultaneous comparisons of different drugs, the assumption of a common slope for the dose–response curves should be examined and logarithmic transformations applied as appropriate.

Pharmacological potency is defined as the inverse molar EC_{50}. It is at EC or ED_{50} where the best precision in a dose–response

TABLE 15 Agreement to tolerability ratio.

Agreement	Misclassification	Agreement to tolerability ratio
Acceptable	One-sided	< 1
Marginal	Two-sided	1–2
Unacceptable	Extreme–extreme	> 2

estimation is found. Up-down sequential allocation is a robust and efficient design to estimate the median effective doses or concentrations and then to estimate potency ratios with 95% CI for two or more drugs.[108] Here patients are randomized to a particular drug and are allocated doses, higher or lower, depending on the response of the previous patient randomized to that drug. Testing then becomes targeted about the eventual ED_{50} and this can be compared to that for other drugs and potency ratios (95% CI) estimated.

4.4.1 | Dose-dependency

Often researchers randomize patients into three or more groups where doses are typically increasing or in ordered categories. They then compare the different doses or groups accounting for multiple comparisons. A more efficient approach might be to perform a test for linear trends across the ordered groups that does not require correction for multiple comparisons. The Cochran-Armitage trend for means or Cuzick trend for medians can thus be used to demonstrate dose–dose dependency.

4.5 | Observational studies—big data

With computational advances in the data mining of complex large population databases, it has become increasingly attractive to researchers to evaluate treatment effects using large data. Data mining is the practice of examining large pre-existing databases with the intention of generating new information. An example is to estimate the effect of NMB on postoperative respiratory complications. One of the problems here is the procedure to match non-randomized patients who received a particular treatment or intervention to another group who did not. The issues of selection and indication biases, measured or unmeasured, do not allow to make inferences about causation, however findings of strong associations can be used for hypothesis-generating approaches. One popular approach to control for such biases is the technique of propensity score (PS) matching.

With PS matching, an analysis of all the patients and variables in the database is performed and an attempt to identify variables that classify patients into comparable groups of interest is performed. This process is usually done using multivariable logistic regression. A PS for a given patient is the conditional probability of being assigned to particular groups or treatments given a set of observed covariates. In practice, the log odds (logit) PS is used as this transformation often approximates normality. Patients are then "matched" to untreated or unexposed controls with similar scores provided that there is reasonable overlap, or common support, of both groups. The treatment or effect size of interest is then estimated. Although PS and other matching techniques allow control for observed variables, there is no such consideration for known unobserved, and unknown latent variables as potential confounders. This can only reliably be addressed by randomization. In the situation where extremes of PS scores cannot be matched, the common support conditions can also lead to censoring and bias.[109]

4.6 | Reporting guidelines

In reporting results researchers should pay attention to the degree of precision reported in relation to the precision actually measured. Descriptive statistics, such as mean and median should be presented with at least one decimal place; SD should be presented with two decimal places, especially if small. *p*-values and correlation coefficients can be presented with two significant digits, with $p < .001$ as the lower limit.

Intention-to-treat analysis, where all randomized subjects are analyzed, irrespective of receiving the correct, or indeed any treatment, is the most robust approach in minimizing confounding due to selection biases. *Treatment-received analysis*, where the subjects are analyzed based on the treatment or intervention received, will give a more accurate estimate of the true-effect size but at the risk of bias from withdrawals after randomization. *Per-protocol analysis*, where only subjects who complete the protocol are analyzed, gives the most accurate estimate of the true effect size, but with the possibility of selection bias.

Authors and researchers should also avail of the EQUATOR (www.equator-network.org) guidelines and use the recommendations appropriate to the design of the study and research hypothesis, examples such as CONSORT for randomized controlled trials, STROBE for observational studies and PRISMA for systematic reviews and meta-analysis.

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DATA AVAILABILITY STATEMENT

The manuscript is a consensus statement, which does not contain shared data.

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