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Adjustable compression wraps: back to the future

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Abstract

Adjustable Compression Wraps (ACWs) are used to treat a variety of conditions, in particular venous leg ulcers, edema and lymphedema. Publications on the use of these devices are ultimately few and far between, with limitations or biases (small sample sizes, methodological weaknesses, non-comparative studies, lack of interface pressures).

A development model like that used in the study of a drug could be more rational. We propose five phases: phase 1) discovery and development, phase 2) in vitro testing, phase 3) clinical trials, phase 4) real-life data analysis, medico-economic investigation using Artificial Intelligence (AI), and phase 5) preparation of regulatory dossiers.

This lack of coherence in development could be an obstacle to widespread clinical use. Using AI to analyse large quantities of data could reduce the cost and number of clinical trials needed to generate more robust evidence.

This would make it possible to better define the clinical effects of ACWs in specific situations (e.g., leg wounds in the elderly, diabetic wounds, mixed leg ulcers, secondary lymphedema of the upper limb, efficacy, and comfort...) and to compare treatment costs between bandages and ACWs.

If we don't explore the future with AI, we'll never know what will be useful for the present - hence the title “Back to the Future”.

Introduction

Compression Therapy (CT) is one of the most effective conservative treatments for lymphatic and chronic venous diseases. We have robust data on the effectiveness of CT only for chronic venous insufficiency (CEAP C3-C6) and lymphedema.[1] The first adjustable compression wraps (Circaid®) appeared in the USA over 20 years ago. Their ease of use is a real progress.[2] Adjustable Compression Wraps (ACWs) are designed to simplify care whether provided by the nurse or the patient. There is, therefore, a paradox between the low number of publications and the interest shown by international opinion leaders. An international survey[3] of the practical use of ACWS by experienced practitioners has shown that their use in relation to their potential use is far from negligible (Table 1).

In effect to date, only 56 publications including "adjustable compression wraps" have been listed in Pubmed, with the aim of studying edema, lymphedema, and venous leg ulcers.

State of the art

After reading these 56 publications, we noted that in lymphoedema, eleven of these studies focused on the efficacy of ACWs on lymphedema. ACWs were able to significantly reduce leg volume and improve lymphedema symptoms. They improved patients' comfort and quality of life. Two Randomized Controlled Trials (RCTs)[4,5] have even shown that their efficacy remains superior or equivalent to Inelastic Bandages (IBs) in the treatment of lower limb lymphedema. Two other RCTs[6,7] in the treatment of breast cancer-related lymphedema showed no difference with an IB. Ochalek[8] expressed doubts about the tolerance of a wrap at the elbow crease in the treatment of upper limb lymphoedema. These RCTs only included a small number of patients.

The other publications were case reports or reviews of limited methodological interest.

In an article published in Veins and Lymphatics, Kroeger K. and Dissemond J.[9] have shown the usefulness of four ACWs in the treatment of chronic venous insufficiency, while emphasizing that control of interface pressure remains a key issue.

In venous edema

A RCT[10] compared the effectiveness of two types of compression devices in reducing chronic venous edema in 36 patients and 40 legs: IBs and ACWs. The authors concluded that ACWs were more effective than IBs in reducing venous edema, especially in the early stages of treatment on Day 1 and Day 7. ACWs with a resting pressure of around 40 mmHg were a more effective therapeutic option than IB with a pressure of 60 mmHg for the treatment of chronic venous edema. No information on the evolution in interface pressures and static stiffness index between D1 and D7 was reported. Comfort was reported to be similar to the two compression devices. The ACWs were readjusted by the patients according to the sensations they felt.

In stasis edema

A RCT[11] involved 30 patients who were treated in one group with an ACW (Circaid Juxtalite®) for 15 days, followed by 15-20 mmHg Compression Stockings (CS) for another 15 days and another group with an ACW for 30 days. The results showed a significant reduction in leg volume (10.8%) in both groups at the end of the 30-day period.

In reducing stasis edema in elderly patients, and importantly, high pressure may not be necessary to maintain results.

In venous leg ulcer

Published data are also scarce. In a systematic review[12] published in the journal "International Wound Journal" in 2019, the authors evaluated the efficacy of ACWs in the treatment of venous leg ulcers and identified 16 articles, including 14 case series, 1 RCT, and 1 audit, reporting on 192 patients. The results showed that ACWs improve healing time, reduce costs by over 50%, reduce the number and length of nursing appointments, and improve patients' quality of life. The authors stress that the level of evidence remains low.

On the other hand, in an Italian multicenter randomized clinical trial[13] published in 2020, the authors evaluated the efficacy and cost of treatment with CircAid® JuxtaCure® for healing venous leg ulcers compared with Coban 2 Layer®.

Sixty-six patients with venous leg ulcers were randomized to treatment with either ACW (n=33) or IC (n=33). No information on interface pressures and Static Stiffness Index (SSI) was provided. The study lasted 12 weeks. ACW was significantly less expensive than IB ($p<0.0001$). They were also more effective (non-significantly) at healing ulcers.

To heal a patient suffering from an ulcer, € 228 was spent in the ACW group and € 381 in the IB group. 78.8% of patients in the ACW group were healed after 12 weeks, compared with 69.7% in the IB group (ns). Ulcer pain was reduced by both compression devices. Patient perception of compression pressure was similar for both devices.

These various studies have shown that the ACWs used pose no problems in terms of comfort (except at the elbow crease). In addition, interface pressures and SSI are never indicated, at least at the time of inclusion.

Mechanical performance of different Adjustable Compression Wraps

A pilot study[14] attempted to assess the mechanical performance of six different ACWs (Coolflex®, Juzo wrap 6000®, Readywrap®, Juxtafit®, Juxtalite® and Compreflex®). The authors evaluated the stretch of these ACWs, their interface pressures in the supine and standing positions, and their SSI. The results showed that Coolflex® is an ACW that could not exceed a maximum pressure of 30 mmHg at rest. Juzo wrap 6000® and Readywrap® have very similar mechanical profiles. The other three ACWs (Circaid Juxtafit®, Circaid Juxtalite®, and Compreflex®) could be applied with pressures in excess of 60 mmHg. In conclusion, this pilot study enables us to propose a classification of ACWs according to their stretch: inelastic ACW, very short-stretch ACWs, and longer-stretch ACWs. A better understanding of the stretch and in vitro stiffness of these ACWs could help to better determine what can be expected of them in clinical practice.

In fact, measurements in healthy subjects[15] and patients with occupational edema[16] may give different SSI measurements when the ACW (ReadyWrap®) is fitted with the same interface pressure. Interface pressure measurements are, therefore, a function of the local radius at point B1, skin hardness, and the adaptation of the ACW to the shape of the leg. For this reason, in clinical trials, in vitro and in vivo data must be specified in the study preamble.

Further research is therefore needed to understand clinical outcomes, assess comfort levels, and secure the long-term use of ACWs. These data are essential if ACWs are to be recognized by health authorities in as many countries as possible.

For a rationale development

In addition, as with IBs, not all ACWs are likely to be comparable in terms of *in vitro* or *in vivo* SSI performance. Therefore, the clinical effects of an ACW of a given brand cannot be extrapolated to an ACW of another brand without in vitro and in vivo controls. This is why an unquestionable clinical development methodology is required. For this reason, each ACW must be developed individually.

On the other hand, we find wraps on the market whose properties are unknown, and some whose clinical effects have not been explored. It would be highly doubtful that a drug whose pharmacological properties, useful dose and tolerance are unknown could be granted marketing authorization.

Unfortunately, obsolete regulations mean that prescribers sometimes have access to compression products whose effectiveness and safety have not yet been proven. Added to this is the fact that the cost of developing an ACW is a real brake.

However, the method used to develop a drug can serve as a rational model for developing ACWs with some adaptations. However, using AI to analyze large quantities of data collected in real life can contribute to development, particularly for gathering economic data.

Drug development phases

The development model used in the pharmaceutical industry[17] provides a framework that could serve as a model for the development of an ACW.

In the pharmaceutical context, there are five development phases (Table 2).

Phase 1: discovery and development

Identification or discovery of a specific molecule that could play a crucial role in a disease. This molecule is likely to produce beneficial and therapeutic effects.

Phase 2: preclinical research

The aim of preclinical research is largely to assess whether a drug is likely to cause serious side effects. Preclinical research also plays a crucial role in determining molecule formulation, including such factors for instance as stability, bioavailability…

Phase 3: clinical research

Clinical research is the next step in drug development, and it serves to test the safety and efficacy of compounds in humans. Clinical research is classically divided into four phases: phase 1, phase 2, phase 3, and phase 4. According to the FDA,[17] phase 1 involves 20 to 100 healthy volunteers or individuals with the disease, phase 2 involves up to several hundred people with the disease, phase 3 involves 300 to 3,000 people with the disease or condition, and phase 4 involves a few thousand people with the disease or condition.

Phase 4: health authority review

Once a drug moves through phase 1, phase 2, phase 3, and phase 4 clinical trials, it advances to health authority review, where a team of experts, including doctors, chemists, statisticians, and other scientists, reviews a drug compound's safety and efficacy findings from its clinical trials.

If the drug is deemed safe and effective for its intended use, the authorities grant approval to manufacture, market, and distribute the drug in their country.

Phase 5: post-marketing safety monitoring

Although clinical research serves to evaluate a drug's safety and efficacy in a relatively small pool of volunteers, it's possible that new concerns may arise in the general population after its approval. That's where a post-marketing surveillance, comes into play.

Adjustable Compression Wrap development phases

The same development process cannot be required for ACWs. However, the absence of a development methodology hampers their use in clinical practice. How can we understand the effect of an ACW if we know little about its physical characteristics (elasticity, stretch, stiffness)?

The same tests cannot be required for the development of an ACW. But the development phases remain essential. (Table 3).

In ACW context given this situation, it remains to be seen what the development phases of ACWs might include.

Phase 1: wrap design

Depending on the morphology, the volume of the limb, the size charts used for compression stockings, and the creativity of technicians trained in textile engineering schools, an ACW

model will be proposed to treat venous-lymphatic pathology. The model thus defined will be tested.

Phase 2: publication of in vitro *tests*

Velcro® fastening and tear-off tests are required. If we consider that an ACW will be applied once a day for several months. The maneuver should be repeated at least 200 times to verify the AWC's durability. Washing tests should also be carried out.

The composition of the materials used is not sufficiently described (polyurethane, polyester, polyamide, nylon, elastane, cotton), particularly as regards the percentages of materials used.

The stretch of the various ACWs remains to be defined (minimum <10%, short stretch from 10% to 100% and long stretch >100%). *In vitro* stiffness is not known (Table 4). It can be calculated using a cylinder or a Hiraï leg,[18] whose circumference is increased by 1 cm when the material is applied. For each increase in pressure from 10 mmHg to 10 mmHg, we can measure the pressure without stretching and with stretching, and thus calculate the *in vivo* stiffness for a given pressure. These measurements can be carried out in the same way as for IB.[19]

Phase 3: clinical development in healthy subjects and Randomized Controlled Trials in patients

In healthy subjects

This phase of clinical study in healthy subjects is crucial. The aim is to evaluate pressure variations, ACW stiffnesses at point B1, limb volume variations, comfort, and tolerance by the subjects over the course of the day.[20]

In this case, a test during daily activities lasting at least 4-5 hours is necessary. This could be replaced by a treadmill test at a speed of 4 km/h and a slope of 8% or coupled with the daily activity test.

No studies have been found on the standardization of the treadmill test used in the venous field. In our experience[20] given the frequency of ankle ankylosis in elderly patients with venous ulcers, the walking perimeter is less than 1km/day, *i.e.*, 2,000 to 2,500 steps/day. It was decided to test the compression device on a treadmill at 4km/h for 15 min, with a slope of 8%. These tests could correspond to the daily activity of an elderly patient suffering from a venous leg ulcer.

The choice of a comparator bandage is an essential element of a randomized limb-versus-opposite limb study. The choice of comparison bandage could be based on the bandage most commonly used for a specific indication in the country concerned (e.g. in France, the bandage most commonly prescribed to treat leg ulcers is Urgo K2®).

In patients with venolymphatic pathology

The stretch of the ACW gives an idea of the achievable interface pressure. An ACW with a stretch of <10% would not achieve an interface pressure of >30 mmHg at rest,[11] whereas with a stretch of 50-60%, higher interface pressures could be applied.

According to a consensus statement,[21] a pressure of <30 mmHg should be applied in the case of edema and 30-40 mmHg in the case of venous ulcers and lymphedema.

Primary clinical objective

For patients with edema and leg ulcers, robust study quality criteria[1] must be met because a blind study is not possible. One clinical indication must correspond to a randomized multicenter trial with a clearly defined primary clinical objective. For example, for a venous leg ulcer, complete healing of the ulcer is the primary endpoint. For lymphedema, the decrease of leg volume will be the primary endpoint.

The secondary objectives are: i) pressure application if integrated pressure sensor in the device; ii) compliance; iii) number of visits; iv) surface of lesions; v) evolution of the volume of the limb; vi) Visual Analog Scale (VAS) for comfort and pain; vii) Quality of Life (QoL) scores and viii) side effects.

Statistical analysis

Calculation (Figure 1) of the number of patients to be included before the start of the trial based on expected results or the results of pilot studies.[22] The number of patients to be included will be taken into account if non-inferiority or a significant difference is to be demonstrated.

Intention-To-Treat (ITT) and Per-Protocol analyses (PP) are mandatory. ITT analysis is especially mandatory in cases of non-compliance and missing results, as well as in terms of safety and tolerance.

The weaknesses of a long-term clinical study are inevitable: interface pressures and stiffness indices (except for adhesive sensors on the skin or sensors integrated into the compression device) are not yet available, as new sensors are under development.

Recruitment difficulties and the cost of studies in Europe are obstacles to carrying out a multi-center randomized clinical trial. The potential sales of an ACW cannot justify the cost of a

clinical study. One solution would be to carry out these studies outside Europe in a country where the procedures are just as rigorous, but quicker and ultimately less costly.

Phase 4: real-life analysis, medico-economic survey with Artificial Intelligence

AI will make it possible to analyze thousands of data (from public and private insurance companies) as part of a medico-economic study comparing the use of a bandage and an adjustable compression. Collecting this data will make it possible to carry out a study under real conditions and at a lower cost.

A concrete example: a study of venous leg ulcers comparing the effectiveness of a branded ACW with that of a branded bandage. The parameters of a classic RCT are numerous: age of the ulcer, recurrence, diabetes, hypertension, lipid disorders, PTS, surface area, depth, stage of the wound, topography, edema, wound infection, cost of nursing care, hospitalization, ultrasound examinations, mixed ulcer, healing time, *etc*. It is, therefore, impossible to study all aspects of venous ulcers. The large number of subgroups makes it impossible to carry out an analysis after a study of a few dozen patients. The analysis of thousands of patients followed in daily practice by AI will enable us to identify differences between the two devices.

Phase 5: preparation of regulatory files

Health authorities, particularly if reimbursement has been requested by the manufacturer, require medico-economic data. Only a real-life study can help to provide such data. Data such as this, together with a dossier built around the objective of reducing healthcare costs, are bound to convince the economists on the official committees.

Discussion

Will the use of AI streamline the development of an ACW and shorten the development time? This is possible, provided that the authorities consider ACW a priority in overall healthcare expenditure (e.g. the National Health System in Great Britain). Advanced chronic venous disease, leg wounds in the elderly, and lymphedema of the upper limb after breast cancer represent a rationalizable cost. The only problem is that the costs involved are poorly understood. ACWs (Table 5) may be part of the solution, given their supposed advantages (long service life, ease of application, adjustable pressure, devices for upper and lower limbs, and self-adjustment by the patient or the caregiver).

In venous pathology: another advantage of ACWs is the absence of compression of the foot and ankle. In fact, ACWs act not distally but mainly at the calf level, increasing the ejection fraction[23] and thus facilitating venous return. This is not the case for lymphedema, where foot compression is often necessary.

As far as AI is concerned, it will undoubtedly become a driving force in the development of compression devices. AI will shorten clinical trials on the target pathology by making it possible to analyze the mega data used in real life. It will streamline clinical trials by identifying eligible patients.

AI algorithms could analyze large amounts of patient data to identify correlations, enabling the development of personalized treatment plans tailored to each patient's needs.

AI insights will optimize resource allocation, reduce waste, and improve the overall efficiency of healthcare systems.

Medical device manufacturers that use AI in clinical development will gain a competitive advantage by bringing innovative solutions to market faster. As such, the adoption of AI in clinical development is key to unlocking new opportunities for growth and innovation for medical device manufacturers.

Authorities will need to adapt over the next few years. A technological and intellectual breakthrough is likely.

Conclusions

Not all ACWs available to prescribers and patients have proven efficacy and safety. Robust clinical trials are few and far between. Furthermore, their results are not generalizable to all ACWs. This article proposes a development methodology like that used for drugs. The use of artificial intelligence to analyze data collected in real life should make it possible to better define the indications for ACWs and, above all, to achieve substantial savings in their development. This development method should make it easier for the health authorities of the countries concerned to take responsibility for the treatment and simplify transnational registrations.

References

1. Mosti G, Wittens C, Caggiati A. Black holes in compression therapy: a quest for data. J Vasc Surg Venous Lymphat Disord. 2024;12:101733.
2. Mosti G., Partsch H. Self-management by firm, non-elastic adjustable compression wrap device. Veins and Lymphatics. 2017;6:7003.
3. Mosti G, Namislo A, Benigni JP, et al. Indications, contraindications, side effects, general assessment, and outlook for the future: an International Compression Club survey. Phlebology. 2024;39:342-52.
4. Damstra RJ, Partsch H. Prospective, randomized, controlled trial comparing the effectiveness of adjustable compression Velcro wraps versus inelastic multicomponent compression bandages in the initial treatment of leg lymphedema. J Vasc Surg Venous Lymphat Disord. 2013;1:13-9.
5. Borman P, Koyuncu EG, Yaman A, et al. The comparative efficacy of conventional short-stretch multilayer bandages and velcro adjustable compression wraps in active treatment phase of patients with lower limb lymphedema. Lymphat Res Biol. 2021;19:286-94.
6. Pujol-Blaya V, Salinas-Huertas S, Catasús ML, et al. Effectiveness of a precast adjustable compression system compared to multilayered compression bandages in the treatment of breast cancer-related lymphoedema: a randomized, single-blind clinical trial. Clin Rehabil. 2019;33:631-41.
7. Silva JMPD, Araújo RDD, Aguiar SS, et al. Efficacy, safety of and adherence to adjustable compression wraps in the control phase of breast cancer-related lymphedema: a randomized controlled trial. Clin Rehabil. 2024:38:1481-94.

8. Ochalek K, Kurpiewska J, Gradalski T. Adjustable Compression Wraps (ACW) vs. Compression Bandaging (CB) in the acute phase of breast cancer-related arm lymphedema management-a prospective randomized study. Biology (Basel). 2023;12:534.
9. Kroeger K., Dissemond J. Chronic venous insufficiency and interest of adjustable compression wrap devices. Veins and Lymphatics. 2019;8:8054.
10. Mosti G, Cavezzi A, Partsch H, et al. Adjustable velcro compression devices are more effective than inelastic bandages in reducing venous edema in the initial treatment phase: a randomized controlled trial. Eur J Vasc Endovasc Surg. 2015;50:368-74.
11. Benigni JP, Uhl JF, Balet F, Chahim M. Treatment protocol on stasis edema in poorly mobile nursing home patients. Int Angiol. 2018;37:396-9.
12. Stather PW, Petty C, Howard AQ. Review of adjustable velcro wrap devices for venous ulceration. Int Wound J. 2019;16:903-8.
13. Mosti G, Mancini S, Bruni S, et al. Adjustable compression wrap devices are cheaper and more effective than inelastic bandages for venous leg ulcer healing. A multicentric Italian randomized clinical experience. Phlebology. 2020;35:124-33.
14. Benigni JP, Uhl JF, Filori P, et al. Adjustable compression wraps: stretch, interface pressures and static stiffness indices. Int Angiol. 2023;42:247-53.
15. Benigni JP, Uhl JF, Taha W, et al. Interface pressures and stiffness indexes before and after a treadmill test of an adjustable compression wrap. Comparison with two compression bandages (in press).
16. Taha W, Benigni JP, Uhl JF, et al. Performance of an adjustable compression wrap in occupational leg swelling. Phlebology. 2024;39:302-9.

17. Tamimi, Nihad AM, Ellis P. Drug development: from concept to marketing! Nephron Clinical Practice 2009:113:c125-31.
18. Hirai M, Partsch H, The mannequin-leg: a new instrument to assess stiffness of compression materials. Veins and Lymphatics. 2013;2:e3.
19. Benigni JP, Uhl JF, Balet F, Filori P. Interface pressures and stiffnesses of different bandages studied on a Hiraï leg. Veins and Lymphatics. 2024;13:12240.
20. Jindal R, Balet F, Filori P, et al. Interest of a standardized treadmill test to evaluate pressure drops and stiffness indices under short stretch bandages. Indian Journal of Vascular and Endovascular Surgery. 2020;7:385-8.
21. Partsch H, Flour M, Coleridge-Smith P. Consensus statement. Indication for compression therapy in venous and lymphatic disease. Intern Angiol, 2008;27:193-219.
22. BiostaTGV. Available from: https://biostatgv.sentiweb.fr/
23. Partsch H, Mosti G. Sport socks do not enhance calf muscle pump function but inelastic wraps do. Int Angiol. 2014;33:511-7.

Table 1. Practical use of wraps by experienced practitioners.

Indications	Compression Stockings	Inelastic Bandages	ACWs	Elastic bandages	Others
C0s, C1s, C2s	86%	2%	2%	5%	
C3-C5	63%	15%	10%		2%
Venous ulcers	9%	79%	12%		
Mixed ulcers	3%	75%	19%	3%	
Lymphedema	10%	73%	15%	2%	

ACWs, Adjustable Compression Wraps

Table 2. Drug development phases.

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Discovery and development	Preclinical research	Clinical research 4 phases	Health authority review	Post-marketing safety monitoring

Table 3. Adjustable Compression Wraps (ACWs) development phases.

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Discovery and development	Preclinical research	Clinical research	Health authority review	Post-marketing safety monitoring
Wrap design	***In vitro* test**	**Clinical development in healthy subjects and RCT in patients**	**Real-life analysis: medico-economic survey with AI**	**Preparation of regulatory files**

RCT, Randomized Controlled Trial; AI, Artificial Intelligence

Table 4. Definitions of stretch and stiffness.

Stretch	Extension of a compression device to its maximum
***In vitro* stiffness**	Variation in interface pressures as cylinder diameter increases by 1 cm

Table 5. Benefits of Adjustable Compression Wraps (ACWs).

Benefits of ACWs according to the manufacturers
Easy application
Variable compression levels available
Upper/lower limbs options
Adjustable by the carer/patient
Can be worn with shoes

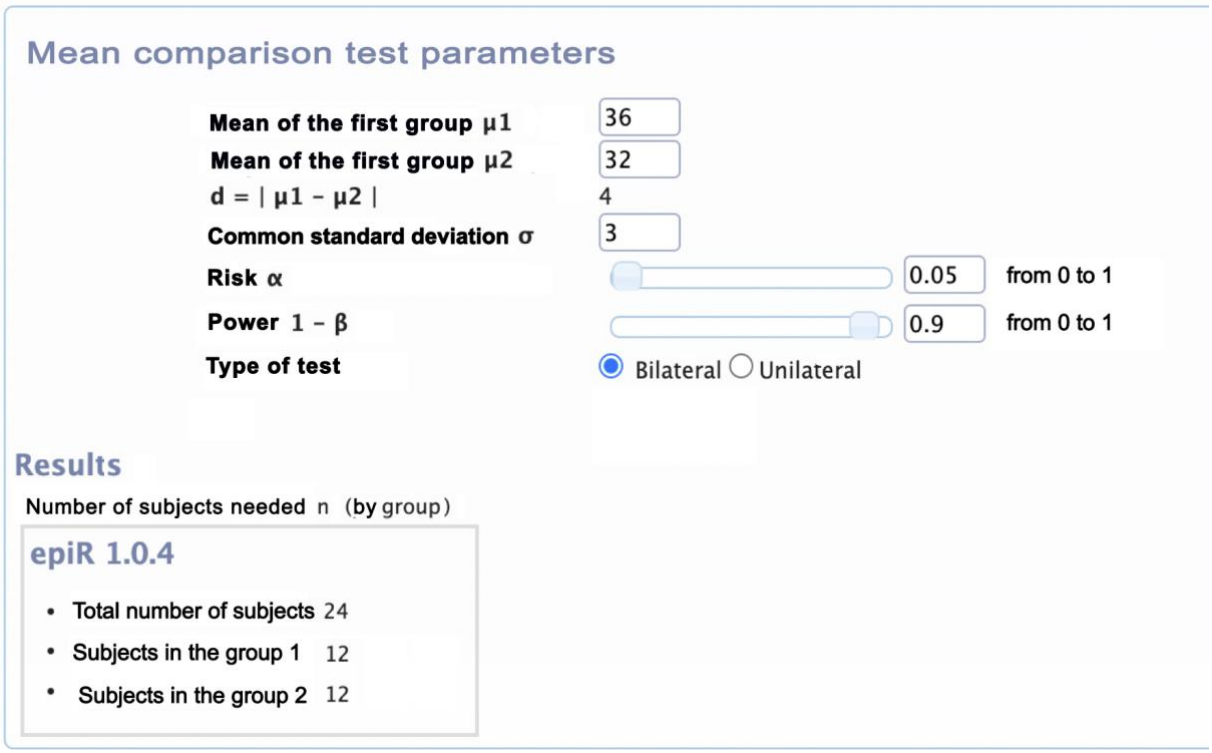

Figure 1. Calculation of the required number of patients based on assumed or observed means.