Clinical Evaluation IRATHERM1000M

of

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of Applied Medical Research GmbH

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1 Summary

2 Scope of the Clinical Evaluation Report (CER)

2.1 Basic properties

Description	Proof
Name:	Hyperthermia-device IRATHERM1000M
Size:	Refer to *M04-1000 Installation Requirements 2020 EN*
Components of the device:	Refer to: *IvA_IRATHERM1000vsIRATHERM1000M Letter* IRATHERM1000M comprises a package of: • IRATHERM®1000 hypothermia device, and • IRAcom® hardware for signal processing, whereas IRAcom® is a transducer system requiring IRAsoft5.0 monitoring software (to be installed on IRATHERM®1000 PC) for acquisition, processing, transmission, display, record and document of various parameters during patient treatment
Equipment group:	Devices for Hyperthermia / Hypothermia
CE Marking Status:	Refer to *109963N5* and *109962M8en*
Countries of distribution:	• Europe (DE, AT, CH, ES, PL, IT, GB, GR, SE) • Asia (CN, TH)
Software version	IRATHERM1000: V4.1 IRAcom: V4.0 IRAsoft5.0: V1.3.2.2
Accessories	Refer to *10AA-70-0000-000 Accessories IRATHERM 1000M_BOM_final*
Manufacturer	Von Ardenne Institut für Angewandte Medizinische Forschung GmbH, Zeppelinstraße 7, 01324 Dresden, Germany

Classification	IIa
Regulations not to be applied	• Particular requirements for sterile medical devices • Particular requirements for implantable medical devices • Particular requirements for active implantable medical devices • Reprocessing of medical devices • Particular requirements for devices containing blood, blood products, blood plasma or blood cells of human origin • Particular requirements for devices containing transplants or tissues or cells of human or animal origin • Particular requirements for devices intended to deliver ionising radiation
Duration of use	10 hours
CE marking	Available since 1998, carried out by "SLG Prüf- und Zertifizierungs GmbH".

2.2 General description

In whole-body hyperthermia with the IRATHERM®1000M, the patient is positioned on a patient bed net. This is located above the six special halogen radiators of the IRATHERM®1000M. The special halogen radiators emit water-filtered infrared A radiation (wIRA), a thermal radiation that hits the back of the patient's body and raises the body core temperature. For thermal and comfort aspects, the patient is covered with a bed sheet and a reflective foil. Furthermore, the patient is connected to up to three temperature sensors (rectal, axillary, superficial) and an ear clip pulse oximetry sensor for monitoring. The upper opening of the reflector box acts as an emission opening for the water-filtered infrared A radiation.

2.2.1 Intended use

The IRATHERM®1000M is a whole body hyperthermia system. It serves to raise the body core temperature up to about 40.5°C within the scope of mild and moderate whole-body hyperthermia. This results in changes in various physiological phenomena, which allow the treatment of patients with different therapeutic aims. In accordance with the spectrum of action of natural fever, the possible use of whole-body hyperthermia is also widely diversified. Relevant literature on this topic is compiled in Appendix 3 of the Instructions For Use.

IRATHERM®1000M is used for the controlled, physiologically sensible increase of the human body core temperature. An increased core body temperature enables activation of blood circulation and relief of

muscle fatigue, muscle stiffness, and muscle pain as well as stimulation of immune system. This happens mainly through:

1 **Activate blood circulation [115, 116]**

Significantly higher tissue blood flow in hyperthermia and to a depth of several cm when using wIRA compared to unfiltered, normal red-light radiation. Persistent improvement in hemodynamics after a series of 12 sessions with core body temperature up to 38.5°C.

2 **Relief muscle fatigue, muscle stiffness, and muscle pain [120]**

With an increase in the core body temperature, and thus also the temperature of the muscles, the oxygen supply to the muscle cells and the cellular ATP turnover increase. This leads to an increase in the contractile performance of the skeletal muscles, stress reduction and detonation.

3 **Stimulation of the immune system [122-128]**

Whole-body hyperthermia contributes to stimulation of the immune system through various physiological mechanisms such as increasing heat shock protein (HSP) expression, cytokine release, dendritic cell activation, and T cell maturation.

2.2.2 Contraindications

- Patients with arteriosclerotic-cerebral contusion
- Hyperthyroidism
- Patients with open cavitary tuberculosis, acute hepatitis, chronic hepatitis, and advanced cirrhosis
- Patients with advanced chronic nephritis and nephrosclerosis
- Acute severe inflammation
- Acute skin heat injury (e.g., sunburn)
- Pregnancy
- Deep intravenous anesthesia, general anesthesia

2.2.3 Higher risk patients and side effects

For the following conditions/ reasons an increased attention by the medical operator is needed:

- Heart failure (hyperthermia may be possible after a mechanical performance assessment and pulse measurement).
- Arrhythmias (ECG monitoring may be possible with hyperthermia).
- acute infection
- People who are prone to heat and spasms.

- Those who are receiving medical treatment that makes their skin more sensitive (e.g., patients using photosensitizers).
- People with low skin heat sensitivity or microcirculation disorders (e.g. diabetic neuropathy, or patients receiving chemotherapy).
- Thrombosis

The following possible side effects can occur while and after a hyperthermia:

- Short-term local skin pain due to overheating, while hyperthermia
- Circulatory problems during hyperthermia
- Irritation of the eyes of the therapist during hyperthermia
- Thermal tissue damage after hyperthermia:
  - Unlikely local deep necrosis under the skin, (grade III burns)
  - Occasional blistering of the skin over small areas, which heals completely (grade II burns)
  - Frequent reddening of the skin, which disappears after two days at the latest (grade I burns).

2.2.4 Intended Patient Group

- The IRATHERM®1000M is intended for the treatment of sick adults. However, health-conscious, healthy adults looking for preventive treatment concepts can also be treated with the IRATHERM®1000M.
- The IRATHERM® is not intended for the treatment of adolescents or children.

2.2.5 Intended User Group

- The IRATHERM®1000M may only be operated by medically trained personnel who have received special training from the manufacturer or an authorised person. The special training of the personnel is carried out during commissioning and/or in case of follow-up training by the manufacturer or an authorised person.
- Operation of the IRATHERM®1000M by the patient is neither intended nor necessary
- IRATHERM®1000M is not intended to be used by unauthorised persons.

2.2.6 Organs, tissues, body parts in contact

During treatment, the unclothed patient usually lies with his back on the patient bed net with his head pointing towards the control unit. The patient's entire back is in contact with the patient bed net. This contact usually remains throughout the entire treatment.

The unclothed patient is covered with a bed sheet (cotton) and a reflective foil, with the head outside the cover. Only the bed sheet makes contact with the entire front of the patient. This contact usually remains throughout the entire treatment/hyperthermia session.

The patient also has contact with the temperature probe. This is positioned in the inner side of the armpit before treatment begins and remains in place for the entire treatment. A second temperature probe, which is usually inserted, is covered with a protective sheath and inserted rectally and also remains in place for the entire treatment.

2.2.7 Usability of the system

The IRATHERM®1000M system is designed for continuous operation. This means that the performance of the hyperthermia system can be provided over an unlimited period of time.

The IRATHERM®1000M system does not require any warm-up time, i.e. the desired radiation output can be called up immediately after switching on.

The IRATHERM®1000M system does not require any cooling time, i.e. the power can be called up again immediately after an interruption or after the end of hyperthermia.

2.2.8 Safety precautions

The manufacturer's safety precautions are divided into the following three categories:

a) Integrated safety through appropriate design
b) Protective measures in the medical device itself and in the manufacturing process
c) Information on safety when setting up the medical device and in the context of therapy management.

Category a) includes the following precautions:

- Safety of the enclosure (metal body, bolted covers).
- Strength of the tube frame (elongation at break, safety factor)
- Safety of the tube frame (end stop)
- Usability of the control unit
- Patient safety (placement of the radiators below the patient)
- Strength of the patient bed net (new development)
- Development of the IRAstep to increase the safety of the patient's ascent
- Design of the spotlight glass tube for increased safety

Category b) includes the following provisions:

- NTC resistor for single radiator monitoring
- Flow sensor for flow monitoring of filter and cooling water
- Aquastop for safe shut-off of the water flow
- Circuit breaker for electrical safety
- Strain relief (mains connection, connection cable IRAcom)
- Factory tests according to protocol specifications
- Commissioning tests according to protocol specifications
- Fabrication of the installations according to written instructions

Category c) includes the following precautions:

User instructions:

- Rules against thermal tissue damage"
- Instruction for Use
- Customer files
- Licht-und-Gesundheit PIAZENA 2012
- M 01b - praxi Tips & Tricks IRA-GKHT onko EN print 2019
- TD_121_DE_KI - Pflegehinweis Patientenliegenetz
- M04-1000 Installation Requirements 2020 EN
- M 08 - Programmablauf mildmodHyp IRA1000 2019 EN

2.2.9 Precautions

- Check the condition and positioning of the patient bed net,
  Remove the net if only one mesh is torn and pull the net up to the bar locking mechanism at the head end,
- Tension the patient bed net right → hand bar to the right of the locking point.
  (danger of thermal skin overload!),
- Before patient enters therapy room → radiator output 30% + air bubble check
  (stress reduction through "sun-flooded room" + air bubbles in the glass filter tube only permissible in mm size!)
- Background music
  (stress reduction by soft music, if necessary brought by the patient),

- Covering of small areas of skin with non-sterile compresses
  ("the more skin wIRA sees → the lower the thermal skin load"
  so "the less skin coverage → the more skin protection"),
  incorrect covering can lead to skin burns and also slow down the rise in core body temperature!
- At least the first 10 ...15 min radiator output 100%.
  (ensure a rapid rise in core body temperature without risk of thermal overload of the skin)
- During the hyperthermia phase, drink still water through a straw.
  (every 10 min ½ glass of water hardly influences the rise in core body temperature,
  as < 1/100 of the body mass),
- Post-rest in a thermally isolated state significantly increases the thermal effective dose (rest for at least ½ h wrapped up in a bathrobe with legs wrapped in a bath towel or, even better, in bed),
- **Patient motivation → T_{goal}**: Whole-body-hyperthermia is not wellness! Chronic illness should be alleviated. The sweaty sessions are stressful but bearable,
- **Heat radiation**: place folded terry towel under head and heels.
  Remove jewellery in the area of radiation, cover scars **and areas with impaired circulation <u>sparingly</u> with non-sterile compresses. (Tattoos** too, if necessary),
- **Warm-up phase**: At least the first 10 ... 15 minutes of therapy at least, set the radiator output to 100% (low-stress hyperthermia phase → introduce as much heat as possible into the body). Then adjust the radiator output in dialogue with the patient,
- **Patient dialogue**: Permanently from the 10th minute of therapy, ask the patient if there is a "**burn**" somewhere on the skin in the radiation area, if so, where? **<u>Regionally</u> reduce** radiant power by ≈15%. Observe the affected skin region.

Measures to avoid or reduce thermal tissue damage <u>before</u> the therapy session

- Complete information of the therapists/nurses by the attending physician regarding previous treatments (surgery, radiotherapy, chemotherapy, photosensitizers ...),
- Check that there are no large air bubbles in the glass filter tubes of the 6 radiators (air bubbles in the mm range)
  (air bubbles in the mm range are permissible),
- Sparing local covering of the circulatory disturbances exclusively with non-sterile compresses,
- Temperature probe cables laid in the radiation area of the water-filtered infrared A radiation must not touch the skin.

Measures to avoid or reduce thermal tissue damage <u>during</u> the therapy session

- Sensitive increase of irradiance in case of altered pain sensation, skin sensitivity and tattoos,
- Observation of the skin with the eye of an experienced therapist,
- For patients at risk, use a radiation pyrometer to observe the skin temperature in the radiation area,
- Permanent questioning of the patient regarding "burning pain" on the skin.
  If "yes", only regional reduction of the radiation intensity, where the pain occurs (!), by about 15%. Ask again after approx. 1 min whether the pain has disappeared,
- Use a spray bottle to briefly spray the painful or reddened skin region with cold water so that heat is quickly drawn out of the skin. Then reduce the irradiance regionally by about 15%. Ask again after approx. 1 min whether the pain has disappeared,
- Apply "panthenol" to stabilise the skin if the skin is already very red.

2.3 Technical specifications IRATHERM*1000M system

- The spectral irradiance of the single radiator is 310 Wm^{-2}.
- The maximum permissible deviation of the irradiance per single radiator is ± 10 Wm^{-2}.
- The spectral irradiance in the treatment area (0.5 m above the radiator axis) is 1300 Wm^{-2}.
- The maximum permissible deviation of the irradiance in the treatment area (0.5 m above the radiator axis) is ± 42 Wm^{-2}.
- The maximum irradiance in the center of the system 0.2 m above the radiator axis is 1550 Wm^{-2}.
- The maximum permissible deviation of the irradiance centered 0.2 m above the radiator axis is ± 49 Wm^{-2}.
- The emitted radiation spectrum is between 400 and 1900 nm.

2.3.1 IRATHERM1000M

1. Main dimensions	
IRATHERM®1000M (LxWxH)	2.500 mm x 870* mm x 850 mm
* … width of base	1.000 mm

Mass:	140 kg
IRAstep (LxW)	600 mm x 400 mm
Monitoring (LxW)	400 mm x 600 mm
Comment:	*Minimum space requirement for IRATHERM®1000M system and patient treatment:* min. 3.500 mm x 2.500 mm

2. Power connection

Nominal voltage	400 V three-phase current (16 A CEE socket)
Protection	3-pole circuit breaker C16, FI-switch
Power consumption	max. 6,9 kW
Connection cable	2,5 m (standard), on request also longer
Potential equalization	Cable (4 mm²) with terminal block or similar

3. Fresh water connection

Shut-off valve	¾" Male thread
Water pressure	min. 2 bar
Flow rate	min. 4 l/min
Hose length	1,5 m (standard), on request also longer
Option:	*For reasons of operational reliability, the use of a ball valve for shut-off is recommended.*
Comment:	*The system is equipped with an Aquastop system analogous to standard household appliances (e.g. washing machine, dishwasher).*

4. Waste water connection

Disposal	∅ 20 mm, with water trap near the fresh water connection
Comment:	*It is possible to use the side outlet at the drain trap of a wash basin.* *The installation of a washbasin is recommended.*

1. Dimensions and weight

Width	40 cm
Length	20 cm
Height	7 cm
Weight (without sensors and cables)	2,5 kg

2. Power connections, system component IRAcom*

Nominal voltage	230 V
Frequency	50…60 Hz
Protection	0,25 A T
Nominal power	5 W
Power Transformer	Input/ output insulation 4 kV
Protection class	SK I
Application section	Type BF
Operating mode	Continuous operation

3. Temperatur sensors (type: TRRE 01-00-2011)

Temperature output range	25°C….45°C
Accuracy	±0,1 K
Resistance (including power)	2252,4 Ω (at 25°C)
Sensor	Pressed ceramic sensor
Connection	¼" Jack plug
Patient Safety	4 kV Separation of user and display section
Length	2,80 m

4. SpO_2 Earclip sensors

Measuring range SpO_2	70%...100%
Operating temperature	-20°C…+50°C
Storage temperature	-40°C…+70°C
Transport temperature	-40°C…+70°C
Rel. air humidity	15…95 % (non-condensing) For operation/ storage/ transport

5. SpO_2 Accuracy

Range	Oxigen saturation A_{rms}[1]
70…100%	±3 digits
70…80%	±3 digits
80…90%	±3 digits
90…100%	±3 digits
SpO_2 Accuracy for weak perfusion	70%...100% ±2 digits (A_{rms}[4])
Accuracy of the pulse frequency	40…240 beats/min ±3 digits (A_{rms}[4])
Accuracy of the pulse frequency range with low perfusion	40…240 beats /min ±3 digits (A_{rms}[4])
Accuracy SpO_2 below 65%	Not specified
Length	2,50 m
Patient safety	4 kV Separation of user and display section

2.4 Fulfilment of needs

The IRATHERM®1000M system is designed to perform mild and moderate whole-body hyperthermia with a core body temperature up to about 40.5°C, with a high tolerability and indication-related duration of therapy application.

[1] ±1 A_{rms} represents approximately 68% of the measurements with an influence of zero.

Possible alternatives to the IRATHERM®1000M system are:

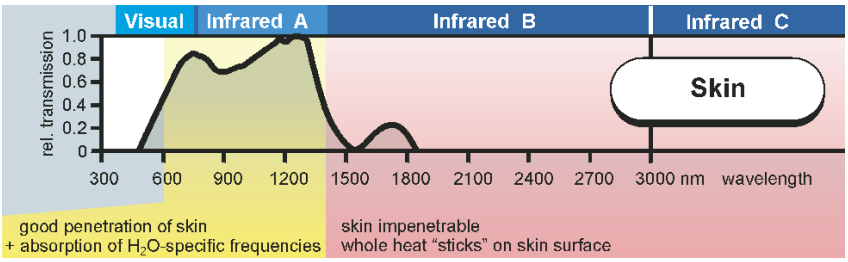
1. whole-body hyperthermia system "heckel-HT3000". This system also uses water-filtered infrared A radiation, but only in locoregional application over the chest. This system has a lower tolerability than the IRATHERM®1000M due to a not inconsiderable proportion of infrared B and C radiation. Furthermore, the duration of the therapy application is unnecessarily prolonged by the lower power of the radiant heaters to the detriment of the patient and the therapist. This system does not allow patient-specific adjustment of the irradiance distribution and places a claustrophobic burden on the patient.
2. warm water baths. Due to the hydrostatic pressure of the warm water, which supplies the body with energy via contact heat, an increased cardiovascular strain can be observed. As a result, this form of therapy has a lower tolerance than treatment with IRATHERM®1000M.
3. Enthermics Medical Systems. This system is no longer available on the market.
4. ET-SPACE. This Chinese system is not available on the European market.

The IRATHERM®1000M system combines various features in one medical device and represents an alternative to the existing hyperthermia systems:

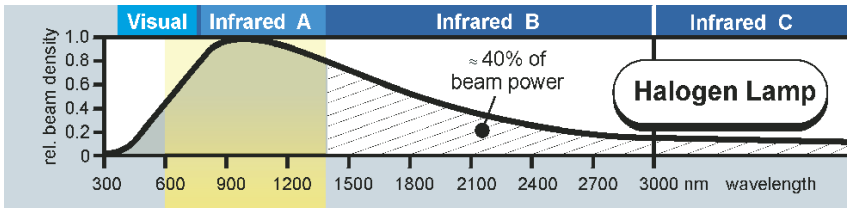
- Rapid rise in core body temperature, despite open design,
- (warm-up phase 30 ... 60 min, with subsequent temperature plateau phase, depending on the target temperature of the indication to be treated),
- High tolerance of heat application (similar to natural solar radiation),
- Open system without claustrophobia, i.e. stress for the patient only in the second half of the warm-up phase,
- permanent eye contact and access of the therapist to the patient,
- High power reserve with regard to irradiation intensity,
- Patient-specific irradiance distribution through six individually controllable radiators between 0...100%,
- Integrated monitoring with software adapted to whole-body hyperthermia, usually no additional devices necessary.

2.5 Physical Description

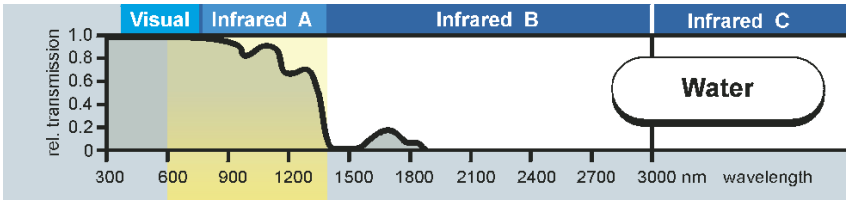
The spectral transmission of skin starts at a long wave visual light of about 600 nm wavelength (see "Visual") and passes the whole infrared-A until its upper long wave limit of about 1,400 nm wavelength. In contrast to that, the skin is nearly impenetrable to heat radiation from the spectral regions of infrared-B and infrared-C. Therefore, one can speak of "deep-acting heat" in the case of infrared-A heat radiation, whereas with infrared-B and infrared–C radiation we speak only of "surface heat".



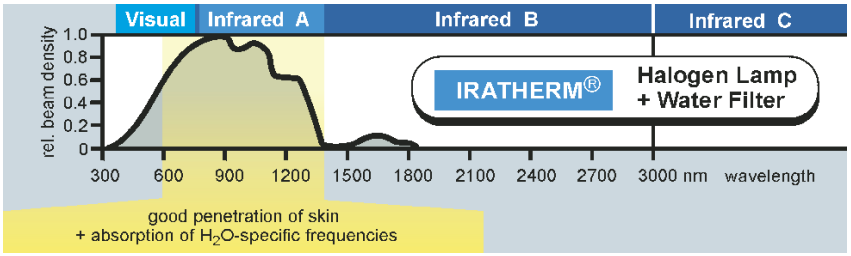
Red light lamps or halogen lamps are well-known and powerful heat radiators. The latter mostly operates on higher power. The following presentation of spectral distribution of a halogen lamp shows that its heat radiation contains 40% of the unwanted, skin–straining infrared-B and infrared–C radiation.



Water is the appropriate choice of filter to eliminate infrared-B and infrared-C radiation because water, similar to skin, has a selective transmission of infrared radiation. This property results from the fact that the skin of an adult consists to 75% of water. Just like skin, water is a good transmitter of infrared-A radiation. While infrared-B and infrared-C are nearly completely absorbed, only small absorption bands (near 950 nm and 1,150 nm) are given in the spectral region of infrared-A.



By placing a water filter in front of a halogen lamp, the result is a heat radiation, with a spectral distribution nearly equal to the spectral transmission of the skin.



Water-filtered infrared-A radiation, as generated by special IRATHERM®-radiators, is a type of heat radiation ideally suited to human skin. Using water-filtered infrared-A radiation the IRATHERM® allows

a much higher irradiation level than that of commercial infrared or halogen lamps at same skin tolerance.

Water-filtered infrared-A is heat radiation similar to natural sun radiation because natural sun radiation is formed with the help of the humid atmosphere of the earth. Over thousands of years, our biggest organ, the skin, has adapted itself very well to water-filtered heat radiation.

2.6 Procedure of Mild and Moderate Hyperthermia IRATHERM®1000M

Before and, if necessary, after completion of mild and moderate hyperthermia, a pre- and, if necessary, post-examination is carried out by the supervising doctor of the center. In particular, an ergometry is carried out beforehand to determine the resilience of the cardiovascular system. Furthermore, the patient will be informed about the treatment. Relaxing background music coordinated with the patient is recommended.
The hyperthermia treatment is as follows:

1 **Before the patient enters the therapy room:** Switch on the system and enter therapy time. Press "START" and set the standby radiator power on 30%. Enter the patient data in the documentation program IRAsoft. Do not forget to enter the name of the therapist! Perform “Bubble Check”, i.e. in the radiators no air bubbles > 5 mm can be seen!

2 **The patient enters the therapy room:** Explanation of the treatment procedure, undressing and possibly showering for pre-cleaning, do not forget the toilet! Doff chains and rings in the irradiation area. Cover scars, tattoos and skin areas of blood-circulation disturbances against direct heat radiation sparingly with multi-layer non-sterile compresses. The patient lies completely undressed on the hyperthermia net and is only covered with a bedsheet and a reflection blanket. Head and heels lie on a folded terry towel. Sensors are placed for permanent monitoring of temperature and pulse. The temperature measurement is carried out usually axillary, additionally rectal at target temperatures > 38.5 °C. The rectally measured temperature is close to the body-core temperature. In intense moderate hyperthermia over several hours, for circulatory stabilization additionally administer inhalative Oxygen[2] and infusions among others. If desired, instead of bedsheet and reflection blanket, an IRAdom may be placed over the patient covered by two reflection blankets.

2 In the upper temperature range of moderate hyperthermia, the **inhalative application of Oxygen** (O_2) of up to 10 l/min is recommended for improving the Oxygen supply to the tissues. It leads to a higher hyperthermia tolerance, especially during the advanced warming-up phase, which, among other things. can be recognized by a pulse reduction.
The combination of moderate hyperthermia and oxygen is equivalent to the **OXITHERMIE®**-designated intensive version of Oxygen Multistep Therapy (O_2MT). After a predetermined premedication, the O_2 application by means of a mask during the hyperthermia phase (about 6 to 12 l/min O_2 flow) and the following e.g. half-hour rest period.

3 **"Start" of hyperthermia:** After completing the preparation phase, press the button "STOP" and 2 seconds later "START". Now the hyperthermia starts with the heating-up phase! This lasts, depending on the indication, over 30 to 60 min or even longer. At least first 10 minutes, better longer, the radiator power should be 100%. Thereafter, according to the patient's condition reduce the radiator power, mostly only reduce regionally. The tolerable water-filtered infrared-A radiation, which penetrates deep into the skin, heats the capillary blood, causing the heat to spread rapidly throughout the body.

Depending on the intensity of the heat intake, individual constitution of the patient and indication, the body-core temperature can be raised up to 40.5 °C and above[3]. This leads in the entire organism to an increase of blood circulation, tissue pO_2 and metabolism. The warming activates the immune system, has a pain-relieving and muscle-relaxing effect.

4 **Permanent care:** The patient is permanently under observation by the therapist during the heating-up phase. Periodically, the patient must be asked about "burning" or "pain" on the skin and if "yes" the radiator power has to be reduced regionally by 15%. 1-2 minutes later ask if "burning" has disappeared, if not, reduce it again by 10%. Furthermore, the face and neck must be cooled with a wet cloth and special observations and activities recorded in the "Logbook" of the IRAsoft. At longer therapy sessions, the patient should be encouraged to move his arms and legs.

5 **Cooling-down phase:** At the end of the heating-up phase plus a possible temperature-plateau phase follows, while lying on the net, depending on the height of the body-core temperature, rest for at least 5 min with reduced radiator power (for example 30%). Removal of all sensors. Then, to reach the orthostasis, slowly sit up on the net for about 2 min in a vertical position. To increase the applied thermal dose after leaving an at least 30 min resting-phase in a recliner, wrapped in bath-robe and bath towel entwined legs, recommended. Thereafter, dry body, if possible use shower and get dressed.

3 Clinical background, Current knowledge, State of the art

The conformity assessment and clinical evaluation shall be carried out on the basis of the following standards, directives and regulations:

- **Directive 93/42/EEC**
- **DIN EN 60601-1:2013**

[3] To ensure a good tolerance of hyperthermia and to **avoid side effects** care must be taken by still inexperienced therapy-guiding staff that the increase in body-core temperature does not exceed 0.6 °C within 10 min!
If the body temperature approaches the predetermined target temperature, the radiator power must be reduced in a predictive manner so that the target temperature is not significantly exceeded.
The first session of a hyperthermia series was to be run with slightly lower average radiator power to learn the patient's individual course of mood and temperature and to introduce him to the hyper-thermia.
A body-core temperature of 40 °C and higher should only be exceeded for special indications and requires usually the observation of the patient by a doctor or naturopath.

- **DIN EN 60601-2-57:2011**
- **DIN EN 80601-2-56:2016**
- **DIN EN 14971:2013**
- **MEDDEV 2.7-1 rev 4**

The following basic physiological phenomena, which are associated with an increase in core body temperature, can be considered as the basis for the indications listed for which whole-body hyperthermia can be used:

A. Promotes blood circulation

B. Relieves muscle fatigue, muscle stiffness, and muscle pain

C. Stimulation of Immune system

3.1 Classification of the selection categories

The classification of the results from the extensive literature research on relevant physiological effects and indications of whole-body hyperthermia is done in two categories.

Category AB:

- Publications with highest and high evidence related to the physiological effects listed above and Publications with highest and high evidence related to the above listed indications of classes I and II of the recommendations of the AHQR (Agency for Healthcare Research and Quality), keyword searched in PubMed,
- Dissertations with high indication-related relevance ,
- Citations from scientific monographs with high indication-related relevance.

Category C:

- Publications that originate from keyword searches in PubMed but are not relevant with regard to the physiological effects and indications listed above.

3.2 Evaluation criteria of the subcategories

The subcategory "methodological quality" of a publication is divided into categories **I** (good) and **II** (less good) on the basis of the 12 evaluation criteria listed below. The expert decides whether a publication receives the "methodological quality" of category **I** or **II** by weighting the 12 evaluation criteria in the context of the respective publication under consideration.

Evicence classes	Journal	Source	Number of patients in intervention group

+	Ia + Ib	**+**	Peer Review	**+**	University and similar	**+**	> 25
0	IIa + IIb	**-**	not Peer Review	**-**	not University	**0**	≥ 10
-	III + IV					**-**	< 10

Inclusion/exclusion criteria		**Valuation methods**		**Appropriate targets**		**Complete patient flow data**	
+	documented	**+**	Good	**+**	Good	**+**	Yes
-	not documented	**0**	Medium	**0**	Medium	**-**	No
		-	Bad	**-**	Bad		

SAE and/or AE		**Follow-up**		**Identity of the device used**		**Discussion with comparable methods**	
+	documented	**+**	has taken place	**+**	Yes IRATHERM1000	**+**	Yes
-	not documented	**-**	has not taken place	**0**	Similar to IRATHERM1000	**-**	No
				-	No IRATHERM1000		

The subcategory "clinical performance of the data" is also classified into a category **I** (good) or **II** (less good). The determination of whether the "clinical performance of the data" receives category **I** or **II** is decided by the expert by evaluating the clinical impact of the results reported in the respective publication.

A final overall assessment is made from the assessment categories **I** and **II** of "methodological quality" and "clinical performance of data". This overall assessment "analysis of clinical data" reflects the relevance of the data set of the respective publication and receives a high relevance A or a lower relevance B. The categorisation is done according to the following scheme.

Methodical quality		**Clinical Performance of the data**		**Total evaluation Analysis of the clinical data**
I	+	**I**	=	**A**
II	+	**I**	=	**A**
I	+	**II**	=	**B**
II	+	**II**	=	**B**

Within the scope of the literature on whole-body hyperthermia that was researched and assessed, not all categories can be answered meaningfully for some publication groups and are therefore marked n grey:

Review / Experimental Study & Basic Biochemical Knowledge

- **Number of patients in intervention group (column K)** rarely stated/irrelevant
- **Inclusion/exclusion criteria (column L)** rarely given
- **Complete data on patient flow (column O)** not or rarely given/irrelevant
- **SAE and/or AE (column P)** rarely stated/irrelevant
- **Follow-up (column Q)** rarely reported/irrelevant
- **Identity of device used (column R)** rarely stated/irrelevant
- **Discussion with comparable methods (column S)** rarely stated/irrelevant

Case report

- **Inclusion/exclusion criteria (column L)** not specified
- **Complete patient flow data (column O)** not provided

German Consumer Report

- **Complete patient flow data (column O)** irrelevant
- **SAE and/or AE (column P)** irrelevant
- **Follow-up (column Q)** irrelevant

Animal Experimental Investigation / Animal Experimental Study

- **Number of patients in intervention group (column K)** irrelevant
- **Inclusion/exclusion criteria (column L)** rarely given
- **Complete patient flow data (column O)** irrelevant
- **SAE and/or ARE (column P)** rarely reported
- **Follow-up (column Q)** rarely reported
- **Identity of device used (column R)** irrelevant

The search criteria with the corresponding publications for the physiological effects and indications as well as additional "literature relevant to the topic that cannot be found in PubMed" can be found in "Overview Literature Search Results".

3.3 Further evaluation methods

Further evaluation methods have been implemented in 2023. In addition to the afore mentioned classification of the "methodological quality" of a publication, we have established flowcharts following the PRSIMA standard [130] to document our literature search approach as well as the evidence classification scheme of Oxford (2009) [131]. The whole process of the clinical evaluation for any project at IvA is designed to follow the concept of true evidence-based medicine (“the best available external clinical evidence from a systematic search”) [129].

3.4 Historical Review

The basic concept of systemic cancer multi-step therapy with the steps of extreme whole-body hyperthermia and induced hyperglycaemia as well as with high-dose oxygen application was already developed in the mid-1960s. At that time, the first experimental experiences and clinical findings on cancer patients after treatment with extreme whole-body hyperthermia were already available by the surgeons R. Kirsch and D. Schmidt in close cooperation with Manfred von Ardenne. Hyperthermia doses of up to 44°C over 60 min were achieved on a smaller number of patients. However, the patient risk was still too high for widespread application. These first treatments were carried out in the Surgical Clinic of the then Medical Academy Dresden, where a special operating theatre had already been set up for research purposes in 1961 by our Biomedical Engineering Department.

Due to the much too early death of our first clinical partners B. Sprung (1963) and R. Kirsch (1971), there was still no decisive and continuous clinical work in the development of systemic cancer multi-step therapy during this period.

A long creative period followed in our institute, which was filled with theoretical work, in vitro experiments and animal experiments. Among many others, the development of a mathematical in vivo theory of the glycolytic metabolism of cancer tumors in 1966, manometric and electrochemical measurements as well as the discovery of the increasing heat sensitivity of cancer cells with decreasing pH value of the tumor microenvironment, but also animal experiments to clarify fundamental questions are to be classified here. In 1969, the systemic multi-step cancer therapy was tested for the first time on the difficult-to-cure DS carcinosarcoma in animal experiments with good results.

As early as 1970, the combination of whole-body hyperthermia (40°C over 250 min) and hyperglycaemia was successfully tested for tolerance in healthy volunteers by von Ardenne, Röhner, Braun and others.

The technique for extreme whole-body hyperthermia has been continuously developed by us over decades. Since our institute was also a manufacturer of heart-lung machines, the idea of extracorporeal hyperthermia by pure infusion of heated blood in a closed circuit was obvious. In 1966 we therefore produced a device for partial extreme hyperthermia by regional perfusion, which was then repeatedly used clinically by I. Navratil in Vienna at the beginning of the 1970s. After the two-chamber tub we designed, manufactured and clinically used in the mid-1960s, we started theoretical and practical work on the construction of a 27 MHz high-frequency hyperthermia device "Selectotherm" in the mid-1970s. With this, a computer-controlled coil applicator was guided contact-free over the body areas to be treated and allowed both the heating of the entire body and a local increase in temperature through increased energy input. This high-frequency system was also used clinically.

Based on all the positive and negative experiences gained up to that time, we developed hyperthermia systems based on water-filtered infrared A radiation in close dialogue with H. Meffert, Dermatological Clinic of the Charité Berlin, from the mid-1980s onwards. This resulted in the whole-body hyperthermia system "IRATHERM®2000" of the third generation, which has been successfully used in clinical practice since 1992 to carry out extreme whole-body hyperthermia as part of systemic multi-step cancer therapy (Systemic Multi-step Cancer Therapy Clinic Dresden, Virchow Clinic, LMU, Gisunt Clinic, etc.).

Pilot treatments at the Charité Berlin of patients with non-oncological indications with water-filtered infrared A radiation on our IRATHERM system, in the mild and moderate temperature range (up to 40.5°C body core temperature), showed surprising, lasting positive treatment results (hypertension, systemic scleroderma). This gave us the opportunity to make whole-body hyperthermia, which has few side effects, accessible to a wider circle of patients. Thus, at the beginning of the 1990s, we began with the development and production of the IRATHERM system. This system was originally developed for non-oncological indications, but is now also in clinical use as an adjuvant measure to activate the immune system in the temperature range of moderate hyperthermia for the treatment of cancer patients.

In the meantime, we have installed over 170 IRATHERM® systems in Europe, with the IRATHERM®1000M being the best-selling system. This system is available in clinics, doctors' surgeries and alternative practitioners' practices as well as in high-class hotels with integrated medical wellness for whole-body hyperthermia.

3.5 Risks of the Whole-body-hyperthermia

Mild and moderate whole-body hyperthermia with core body temperatures up to 40.5°C generally causes few side effects - serious complications are extremely rare. Possible side effects here are:

- Short-term local skin pain due to overheating, while hyperthermia
- Circulatory problems during hyperthermia
- Irritation of the eyes of the therapist during hyperthermia
- Thermal tissue damage after hyperthermia:
  - Unlikely local deep necrosis under the skin, (grade III burns)
  - Occasional blistering of the skin over small areas, which heals completely (grade II burns)
  - Frequent reddening of the skin, which disappears after two days at the latest (grade I burns),

Whole-body hyperthermia with water-filtered infrared A radiation can also be carried out for patients with a pacemaker or implantable defibrillator. Even if there is a metal joint prosthesis in the area to be treated, hyperthermia can be carried out without endangering the patient.

Serious side effects rarely occur with hyperthermia. More frequently, there is short-term pain, redness or swelling in the area of the heated tissue. Burns are very rare. Severe side effects can occur if the skin is not thermosensitive, e.g. after chemotherapy-induced polyneuropathy, or if the skin is more thermosensitive, e.g. after taking St. John's wort.

The phenomenon of the formation of "hot spots" within the body, known from RF hyperthermia, is excluded in whole-body hyperthermia with water-filtered infrared A radiation.

4 Evaluation of the device

4.1 Type of evaluation

The clinical evaluation is based on the review of the currently available literature. A complete literature list can be found in the document "*Overview Literature Search Results*". The individual data sets (publications, dissertations, scientific monographs) were reviewed and analysed according to the criteria mentioned in points 3.1 and 3.2.
The claim to achieve the physiological effects mentioned in point 4.5.3 by increasing the body core temperature by means of water-filtered infrared A radiation up to 40.5°C, in order to achieve relief and in the best case lasting relief of the indications listed in point 4.5.2, is adequately achieved with the IRATHERM®1000M whole-body hyperthermia system. This statement is substantiated by scientific investigations and studies and confirmed by more than 20 years of experience of users in clinics and practices. The claim underlying the IRATHERM®1000M system is therefore fulfilled.

4.2 Clinical data generated and held by the manufacturer

Clinical data generated by the manufacturer are:

- Incident reports
- Error logs
- Self-test protocols of hyperthermia sessions of our institute
- Technical changes to the IRATHERM®1000M system

Incidents that we receive in writing from IRATHERM users are immediately processed, reviewed and documented. The report template ("*Feedback report template*") serves as an aid for the customer and contains all relevant key points for documentation.
Reportable incidents are reported to the responsible authorities.

Error logs are created and documented for all available systems (with a maintenance contract) in the event of an incident. In addition to those incidents that have led to personal injury or damage to property, incidents that could result in possible personal injury or damage to property are also documented. A detailed list can be found in the document "*Journal – Repairs and Feedback*".

Protocols of hyperthermia sessions in the sense of self-tests by the management and staff of our institute are documented and serve to prove the safety of the device and that no serious side effects occur.

All technical modifications to the IRATHERM®1000M system are recorded in the document "*Modification Journal*". All changes were made in close consultation with our Notified Body (SLG) and were checked and approved by them as part of the conformity assessment.

4.3 Clinical data extracted from the literature

The search and selection of relevant literature for the application of whole-body hyperthermia using IRATHERM®1000M takes place within three main groups:

1. Literature search in **PubMed**, the largest database of biomedical literature with 27 million cited medical publications, which includes **MEDLINE** and is linked to **PubMed** Health.
   The **EMBASE** database, which provides mission-critical biomedical literature from "pharmaceutical, medical and life sciences organisations", also includes **MEDLINE**. No systematic review on whole-body hyperthermia was found in the Cochrane database. The most comprehensive results on whole-body hyperthermia were displayed in **PubMed**. Subsets of these were found in the smaller volume of citations in the other databases. Since a selective control search outside of **PubMed** did not find any citations on the hyperthermia topic relevant here, in particular whole-body hyperthermia, with higher evidence, the database literature search could and can be limited exclusively to **PubMed**.

2. Medical dissertations

3. Medical congresses, conferences and symposia

The **PubMed** search carried out in the context of point 1, with a high hit rate in some cases, makes it necessary to divide the data into three categories:

A Whole-body hyperthermia-relevant publications with the highest level of evidence, cited in the context of the clinical evaluation.

B Whole-body hyperthermia-relevant publications with high evidence, cited in the context of the clinical evaluation.

C Publications that are offered in the PubMed literature search but do not represent whole-body hyperthermia-relevant publications.

The above-mentioned categories **A**, **B** and **C** are not used for the above-mentioned main groups point 2. and point 3. On the one hand, dissertations are not yet recorded in an international, central database, on the other hand, those dissertations on whole-body hyperthermia are usually known promptly in the still relatively small international community of hyperthermians. The same applies to medical congresses, specialist conferences and symposia on hyperthermia, which are currently still

concentrated in a few societies, such as the STM, ESHO, ASHO, ICHS and DGHT. The lectures/research results published in the congress volumes and the symposia are systematically evaluated in our institute with regard to whole-body hyperthermia and included in our bibliography if they are relevant and of sufficient quality/evidence. The search terms used are essentially:

- hyperthermia
- whole body
- fever
- perfusion
- blood flow
- oxygen consumption
- kinetics
- tissue
- physiology
- metabolic changes
- synthesis
- growth hormone
- prolactin
- hyperthermia immunology
- heat shock protein 70
- IFN
- natural killer cells
- CD8 T cell
- lymphocyte trafficking
- muscle temperature
- muscle regeneration
- temperature frequency
- nerve conduction
- electrical current
- velocity
- infrared
- human
- hypertensive patients
- chronic back pain
- ankylosing spondylitis
- systemic scleroderma
- major depressive disorder
- seasonal affective disorder
- fibromyalgia
- cancer

A detailed list of the search terms in connection with the respective indications can be found in the document "Overview Literature Search Results". This document also lists the search results, their number and type.

With exceptions for physiological questions, the period of the literature search begins in 1986, since the development of the whole-body hyperthermia system of the IRATHERM® type with water-filtered infrared A radiation was carried out from that year onwards.

4.4 Summary and evaluation of the clinical data

The summary of scientifically relevant literature as well as the assessment of the methodological quality and clinical relevance of each data set is provided in the document "*Overview of literature search results*".

4.5 Analysis of the clinical data

4.5.1 Safety requirements (MDD ER1)

The IRATHERM®1000M whole-body hyperthermia system was designed by an external industrial designer in close cooperation with our Biomedical Engineering department, taking into account both ergonomic and technical aspects. The IRATHERM®1000M systems have been in operation in practices and clinics for 22 years and have proven themselves in clinical practice. Since their market launch, all IRATHERM®1000M systems have been supported by the "Von Ardenne Institut für Angewandte Medizinische Forschung GmbH" (IvA). For each unit, all relevant technical information is recorded in the "*Unique Device Identification*" file (UID) for life and additional information is collected in "customer files". Furthermore, a "*Journal - Repair and Feedback*" is kept in which all repairs, defects and component changes are documented.
Ongoing evaluation of the information gathered indicates that the use of IRATHERM®1000M systems under the intended conditions and for the intended purposes does not endanger the clinical condition and safety of patients, nor the safety and health of users or third parties, as applicable.
Potential risks associated with the intended use include thermal tissue damage. So far, these have been caused exclusively by treatment errors on the part of the personnel, but not by the function of the IRATHERM®1000M. The thermal tissue damage is estimated to have a probability of occurrence of >1000 operating hours/year (OS/year). In the context of the intended use of the IRATHERM®1000M, the risks are considered acceptable in relation to the benefits for the patient.
The technical knowledge and prerequisites for safe operation of the system are imparted to the user during commissioning and in the course of follow-up training.
The undesirable side effects during clinical use of the IRATHERM®1000M do not lead to unacceptable risks, taking into account the specified performance and the recommended program sequence (see point. 2.6).

The IRATHERM®1000M system does not have any special design features that present particular safety concerns.

The known and documented risks associated with the IRATHERM®1000M system are:

- 1st degree burn
- 2nd degree burn
- 3rd degree burn
- Bruises
- Eye irritation
- Skin irritation
- Ingestion of small parts
- Infection
- Electrical accident

The risks were identified through the "Risk Management File" (RMF) and assessed through the "*Failure Mode and Effect Analysis*" (FMEA). The risks were proven to be controllable by practical experience.

The plant design of the IRATHERM®1000M and the associated plant safety were increased to such an extent that the probability of occurrence of risks can only be classified as "remotely conceivable" or "unlikely" ("*overview probability of occurrence*"). A risk that cannot be completely controlled remains 1st and 2nd degree thermal tissue damage caused by operating errors of the therapy guides or inadequate patient information. Incorrect or insufficient transfer of know-how in the event of a change of personnel, creeping routine or carelessness on the part of the personnel can be reduced by the manufacturer within the scope of commissioning, follow-up training and maintenance, but cannot be completely ruled out. Based on the current state of technology, further development to reduce the severity of damage is not possible.

4.5.2 Determination of an acceptable benefit / risk profile (MDD ER1)

It is estimated that about 740 patients have been exposed to the IRATHERM®1000M system in all of the 74 references listed. Together with the approximately 12,500 treatments per year carried out in everyday practice, this results in a sufficiently large number of patients treated with whole-body hyperthermia.
The RMF shows that risks are mainly due to 1st and 2nd degree burns. These occur with a "remotely imaginable" or "improbable" probability of occurrence ("*overview probability of occurrence*"). The operating hours determined in the years 2013 to 2016 serve as evidence. The average number of operating hours is 12,513 h per year. With an approximate therapy duration of 60 minutes, this corresponds to approximately 12,500 treatments per year ("*Overview of operating hours*").

The reported incidents are collected in an "incident journal". This shows that one incident is reported per year. If one extrapolates this incident to the determined therapies, an incident occurs with a probability of 1/12,500 per year. This means that in everyday practice, these risks occur with a probability that lies in the per thousand range.

The probability of occurrence of the risks is reduced as far as possible by appropriate measures.

The duration of follow-up for non-oncological treatments is approximately 30 min after the end of the hyperthermia session. For oncological applications, the duration of follow-up is approximately 3 h after the end of the hyperthermia session.

No undesirable or serious adverse events occurred in the temporal context of the clinical trials.

The assessment of the available information material showed that all relevant instructions are presented to the user in a detailed and clearly understandable manner. In particular, all known risks and side effects for the user are presented in the information materials and operating instructions issued.

The positive clinical results after patient treatments with the IRATHERM®1000M for various indications, for example the improvement of the quality of life, are offset by the relatively low and relatively rarely occurring risks. This results in an acceptable benefit-risk profile with regard to the IRATHERM®1000M system.

4.5.3 Demands on the performance (MDD ER3)

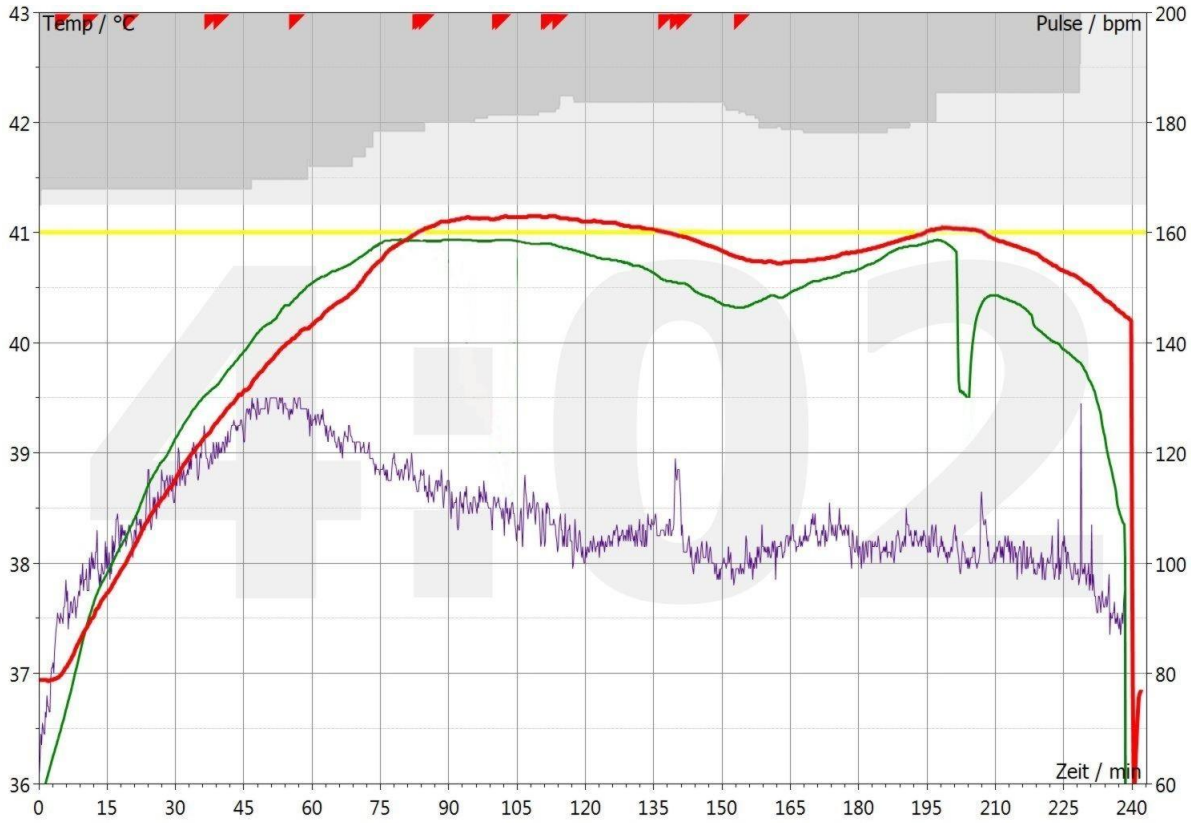
The intended benefits of the IRATHERM®1000M system are:

1. Realisation of an irradiance in the treatment area (0.5 m above radiator axis) of at least 1300 Wm^{-2} and setting of an individual irradiation profile.
2. Increase of the body core temperature up to 40.5°C
3. Alteration of the following physiological processes in the human organism
    a. Activate blood circulation
    b. Relief muscle fatigue, muscle stiffness, and muscle pain

The realisation of the irradiance is always verified within the framework of the institute's own measurements and has been confirmed by our Notified Body "SLG Prüf- und Zertifizierungs GmbH" in Hartmannsdorf. The proofs are recorded in the documents "*AN Superpositionsfaktor.xlsx (IRA1000_V4.0 (1,0kW))*" and "*5021-16-PP-16-PP001*".

The increase of the core body temperature up to 40.5°C has been proven by clinical data. Another indirect confirmation is provided by the approximately 12,500 treatments per year with the

IRATHERM®1000M system, which result from the evaluation of the operating hours ("*Overview of operating hours*"). The following graph serves as an example of a possible, even somewhat higher temperature curve.



The review of the available literature has shown that changes occur for the following physiological phenomena:

a. Activate blood circulation

- The most important physiological parameter that influences the tissues when the temperature increases is the blood flow. This increases, for example, the partial pressure of O2 in the tissues (Horsman 2006, literature search results/perfusion increase organs.../PubMed-Search 1/No. 13).
- Proof that water-filtered infrared A radiation has a significantly better penetration depth into the skin as well as better tissue perfusion than normal halogen radiation (Hellige 1995, Literature search results / Perfusion enhancement organs.../ Topic-relevant literature/No. 2)
- Even 4 weeks after the series of sessions, the flow properties and peripheral blood circulation were significantly improved (Bäumler 1990, Literature search results / Perfusion increase organs... / Literature relevant to the topic / No. 3).

b. Relief muscle fatigue, muscle stiffness, and muscle pain

- Hyperthermia decreases the neural activity of the human cortical somatosensory processing. On the other hand, increasing body temperature (hyperthermia) accelerates swelling signals from the periphery to the cortex (Nakata 2015, Literature Search Results/Muscles and Nerves/PubMed-Search 3/No. 2).
- Moderate hyperthermia (39°C) promotes the growth of sarcomeres in myofibrils at the late stage of myogenesis. The genes of myofibrillogenesis, myosin, actin, nebulin and titin are all upregulated in moderate hyperthermia compared to a control cell culture at 37°C. After thermal exposure of myoblasts, mitochondrial biogenesis is increased (Guo 2016, Literature Search Results/Muscles and Nerves/PubMed Search 4/No. 9).

c. Stimulation of the immune system

- Hyperthermia stimulates the immune system by several mechanisms. One of the main mechanisms is that it can increase the expression of heat shock proteins (HSPs), which act as danger signals to alert the immune system. HSPs can also enhance antigen presentation, activate dendritic cells, and promote the maturation of T cells, which are important for initiating and maintaining an effective immune response against cancer.
- Additionally, hyperthermia can increase the infiltration of immune cells into the tumor microenvironment and enhance the sensitivity of cancer cells to cytotoxic agents and radiation, which can further stimulate the immune system to attack cancer cells.

4.5.4 Determination of acceptable side effects (MDD ER6)

It is estimated that about 740 patients have been exposed to the IRATHERM®1000M system in all of the 74 references listed. Together with the approximately 12,500 treatments per year carried out in everyday practice, this results in a sufficiently large number of patients treated with whole-body hyperthermia.
The RMF shows that risks are mainly due to 1st and 2nd degree burns. These occur with a "remotely conceivable" or "improbable" probability of occurrence ("*Overview probability of occurrence*"). The operating hours determined in the years 2013 to 2016 serve as evidence. The average number of operating hours is 12,513 h per year. With an approximate therapy duration of 60 minutes, this corresponds to approximately 12,500 treatments per year ("*Overview of operating hours*").

The reported incidents are collected in the "*Journal - Repairs and Feedback*". This shows that one incident is reported per year. If one extrapolates this incident to the determined therapies, an incident occurs with a probability of 1/12,500 per year. This means that in everyday practice these risks occur with a probability that is in the per mille range.

The duration of follow-up for non-oncological treatments is approximately 30 min after the end of the hyperthermia session. For oncological treatments, the duration of follow-up is approximately 3 h after the end of the hyperthermia session.

Adverse or serious adverse events have not occurred in the temporal context of the clinical trials.

5 Conclusion

The comprehensive clinical evaluation of the IRATHERM®1000M whole-body hyperthermia system, with the focus on the medical device itself, as well as its use in various indications, allows the following summarised conclusions:

- The essential requirements of IEC 606001-1 specified in Annex ZZ are met.
- The evaluation of the basic requirements has shown that they are sufficiently fulfilled and documented.
- The positive clinical results after patient treatments with the IRATHERM®1000M in various indications, for example the improvement of the quality of life, are offset by the relatively low and relatively rarely occurring risks. This results in an acceptable benefit-risk profile with regard to the IRATHERM®1000M system.
- The evaluation of the available information material showed that all relevant information is presented to the user in a detailed and clearly understandable way. In particular, all known risks and side effects for the user are presented in the information materials and operating instructions issued.
- The increase of the body core temperature up to 40.5°C has been proven by clinical data. Another indirect confirmation is the approximately 12,500 treatments per year with the IRATHERM®1000M system, which result from the evaluation of the operating hours.
- The claim to achieve the physiological effects mentioned under point 4.5.3 by increasing the body core temperature by means of water-filtered infrared A radiation up to 40.5°C, in order to achieve relief and in the best case lasting relief of the indications listed under point 4.5.2, is adequately achieved with the IRATHERM®1000M whole-body hyperthermia system. This statement is substantiated by scientific investigations and studies and confirmed by more than 20 years of experience of users in clinics and practices. The claim on which the IRATHERM®1000M system is based is therefore fulfilled.

- Clinical data show positive clinical results after patient treatments with the IRATHERM®1000M for various indications, with relatively low and relatively rarely occurring risks. The available information material is presented in detail and clearly understandable. The existing hazards are assessed and presented in the RMF. We have currently come to the conclusion that the medical benefits justify the existing hazards and that further minimization of the risks is not necessary. Based on the above information, consistency is assumed between clinical data, information materials provided and RMF.

- The management has decided that the overall residual risk is acceptable. In order to explicitly point out the risks, symbols have been inserted in the currently valid instructions for use for the IRATHERM®1000M, which are intended to draw the therapist's attention. The evaluation method and criteria for the acceptance of the overall residual risk are recorded in the document **Roles_RACI-Matrix**.

Thus, the whole-body hyperthermia system IRATHERM®1000M fulfils all relevant points.

6 Date of the next clinical evaluation

The IRATHERM®1000M systems have been in operation in practices and clinics for 22 years and have proven themselves in clinical practice. A new clinical evaluation of the IRATHERM®1000M system is carried out when one of the following points occurs:

1. Changes in the legal framework conditions
2. Changes to the plant design or the manufacturing processes
3. Feedback from the PMS that gives cause to reconsider the current assessment.
4. In a maximum of 5 years, as the IRATHERM®1000M system is a device that does not pose significant risks and is well established.

7 Qualification of responsible reviewers

Lead reviewer: Dr. rer. nat. Alexander von Ardenne

Dr. Alexander von Ardenne holds a doctorate in physics in the field of electron optics (TU Dresden). As early as 1975, he gave his first medical lecture at the "International Symposium on Oxygen Transport to Tissue" on substrate consumption in cancer tissue. During this time, he also published papers on oxygen and glucose diffusion in cancer tissue and in the myocardium as well as on pharmacokinetic aspects of cancer tissue damage in the "Zeitschrift für Naturforschung", "Akta Cardiologica" and in "Arzneimittel-Forschung". In 1993, Dr. A. von Ardenne took over the management of the "Von Ardenne Institut für Angewandte Medizinsche Forschung GmbH" in Dresden together with Prof. Manfred von Ardenne and continued to work in the same function after the death of Prof. M. von

Ardenne. Since this time, the research and development of whole-body hyperthermia as well as the clinical testing of the "systemic multi-step cancer therapy" developed by Prof. M. von Ardenne was essentially in the hands of Dr. A. von Ardenne. With his collaboration, the scientific monograph by Prof. M. von Ardenne "systemic multi-step cancer therapy" (1997), a peer-reviewed publication on "whole-body hyperthermia with water-filtered infrared radiation" in Int. J. Hyperthermia (2001) and a chapter on "extreme whole-body hyperthermia with water-filtered infrared radiation" in the scientific monograph by Baronzio GF, et al. Locoregional radiofrequency-perfusional and whole-body hyperthermia in cancer treatment: New clinical aspects. Georgetown: Landes Bioscience (2005). In 2016, Dr. A. von Ardenne received the DGHT Award of the "German Society for Hyperthermia".

Second Reviewer: Noah Molinski, M.Sc.

Mr. Noah Molinski worked as a further reviewer of the IRATHERM® medical device family. Mr. Molinski graduated with a Master of Science degree in Physics from the University of Göttingen and TU Braunschweig. He has been actively engaged in scientific research since 2017 and joined IvA in 2020 as Manager Applied Research. The main area of responsibility includes technical development and medical research as well as scientific lectures. He is characterized by very good knowledge of regulatory requirements (including certification as auditor for quality management according to DIN EN ISO 13485 (1st/2nd party) since 2021, participation in internal audits since 2020) and postgraduate experience in scientific writing through several own publications. In addition to proven knowledge of "Good Scientific Practice" (certificate of participation-GSP-Charité), working in technical development also provides sufficient product-specific expertise on the IRATHERM® systems to assume the role of the main reviewer in this clinical evaluation.

8 Expression of interest of the reviewer for the literature review/assessment IRATHERM®1000M.

The evaluation or assessment of the relevant literature researched for whole-body hyperthermia with IRATHERM®1000M was carried out by the managing director of the "Von Ardenne Institut für Angewandte Medizinische Forschung GmbH", Dr. rer. nat. Alexander von Ardenne, to the best of his knowledge and belief. His many years of monitoring scientific work and his own publications leave no room for conflicts of interest, as he feels exclusively committed to the well-being of the patient, which is at the end of all therapeutic application of hyperthermia systems. Based on this basic understanding, conflicts of interest, such as mercantile interests, are irrelevant in the context of the assessments and evaluations mentioned.

9 References

The literature references mentioned in points 4.5.2 and 4.5.3 can be found in the document "*Overview Literature Search Results*".

All referenced documents mentioned in this report can be found in the document "*Table of Contents*".

10 Literature

Introduction

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11 Revision History

Date	Editor	Comment	Revision
09.05.2017	G. Günther	Generating the document	00
19.01.2021	G. Günther	Deletion of the six indications and focus on two modes of action ("Activate blood circulation" & "Relieve muscle fatigue, muscle stiffness, and muscle pain")	01
24.03.2021	G. Günther	Addition to the literary list (10). Reassignment of the indications (2.2.1) to the literature list (10).	02
25.04.2023	N. Molinski	Addition of intend use “Stimulation of Immune system” & section “Further evaluation methods“.	03