

Managing risk in Cryopreservation



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Managing risk in Cryopreservation

- Define risk
- How to identify/quantify risk
- Risk associated with Cryopreservation
- Specific examples and controls

What is risk?

- Risk - Probability of an adverse event or hazard
- Risk Categories
 1. The unavoidable - spontaneous e.g. flood, fire, aliens, management involves coping with the consequences
 2. Compliance with standards - known, planned for, manageable e.g. Accreditation, Regulation (EUTD)
 3. Avoidable risks - can be predicted and therefore controlled

Unavoidable Risk

- Dynamically derived events e.g. infections, epidemics, manmade or natural disasters
- Will occur at some point despite risk avoidance measures
- Outcomes are about coping with the consequences - contingency planning (what if.....)



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Compliance with Standards

Voluntary e.g. best practice guidance

Mandatory schemes - EUTD

- Accrediting/licensing bodies
 - ISO
 - HFEA (UK)
 - AATB, CAP (US)
 - RTAC (Australia/NZ)
- Medical Devices
 - FDA approval
 - CE marking
- Zero tolerance - Check compliance by audit

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Avoidable Risk



- Found by: observation, common sense, past experiences
- RM benefits from an open (no blame) reporting culture
- Learning from mistakes - near miss/incident reporting

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Failure to control risk

- Loss of Material (patient, research)
- Errors in ART

- Loss of reputation/referrals/contract
- Loss of license
- Loss of business

- Loss of fingers, toes, eyes, life.....

Formal Risk Identification

• Risk Assessment

Method for early identification of adverse events (hazards)

- Implement controls
 - SOPs
 - training
 - equipment
 - facilities

- reduce the chance of those occurring
- reduce insurance premiums

Assessing risk

- Risk Assessment - difficult (prior knowledge)
- Break down the process
 - Areas/rooms e.g. cryoroom
 - Process/Procedures

- Incidents - i.e. actual occurrences
 - probability can be estimated
 - Controls implemented for future
 - Open reporting culture essential

'Learn by your mistakes and those of others'

Risk Quantification

AZ/NZ54360:1999

(risk = consequences x likelihood)

CONSEQUENCES	PROBABILITY					
	Impossible 0	Rare 1	Unlikely 2	Moderate 3	Likely 4	Certain 5
Negligible - 0	0	0	0	0	0	0
Minor - 1	0	1	2	3	4	5
Serious - 2	0	2	4	6	8	10
Major - 3	0	3	6	9	12	15
Fatality - 4	0	4	8	12	16	20
Multiple Fatalities - 5	0	5	10	15	20	25

- 'Risk associated with Cryopreservation'
- The biggies!
 1. Injury to personnel
 2. Loss of stored material
 3. Damage to stored material
 4. Misidentification of material
 5. Risk to recipient/ART errors
 6. Financial
 1. Litigation (loss of patient material)
 2. Loss of research material
 7. Failure to comply with regulation
 8. Loss of Quality Assurance

Risk

Injury to personnel
Loss of stored material
Damage to stored material
Misidentification of material
Risk to recipient/ART errors
Financial
Quality assurance/user satisfaction
Regulation

Area of service

Process
Procedure
Area or room

Causative factors

Natural events (Floods/Fire/terrorism)
Technical/training
Professional liability/Human error
Infection Control
Staffing Issues
Facilities (nitrogen transport and storage)
Product and equipment liability
Security (specimens, facilities, data)
Resources

Injury to personnel



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Injury to personnel



Hazards

1. Death (asphyxiation)

- Classed as a simple asphyxiant
- Stored as a liquid
- Revert back to gas very quickly
- 700x expansion LN₂ to gN₂
- Colourless, odourless, tasteless

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Injury - Pressurised vessels



- Tank Explosion Japan (1992) - fragments projected 350 metres
- Investigation
- Relief valves closed
- No manuals/operating procedures/safety instructions/training
- No daily inspections

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Injury to personnel Transport of Nitrogen

- Pressurised vessel
 - toppled over' trapping a porter underneath
- Transport in elevators
 - Emergency venting (burst disc)
 - Lift threshold
- Transport by hand
 - Dewars carried by hand (full) upstairs
 - Dilvac

Transport and elevators
• British Compressed Gas Association
<http://www.bcga.co.uk/>

Injury to personnel Other

1. Burns

PPE, emergency procedures



2. Explosion

- Flasks
- Cryovials
- Ice plugs



Injury to personnel

Explosion Cryovials - shrinkage and embrittlement in LN2

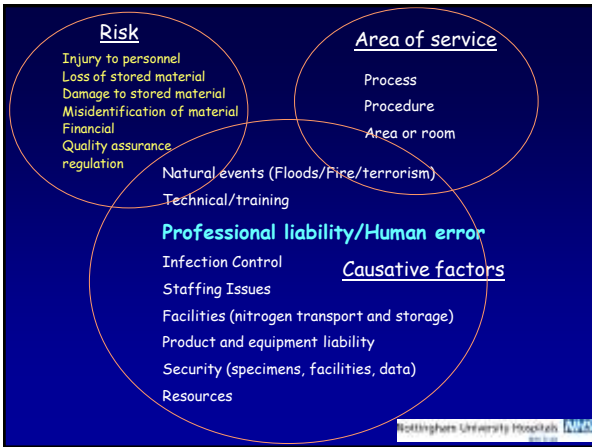


"0.5ml LN₂ in a 1.5 ml vial = 4,053 psi on evaporation
Failure of the seal - projectile with an initial velocity of up to 296 miles per hour (132 meters/sec) ~ 3.4% kinetic energy of a 22-calibre bullet!"

[American Industrial Hygiene Association](#)

1. Letter From A Nobel Prize Laureate on The Loss of Sight In One Eye Due To A Cryogen Accident ([top](#))

70% UK embryologists observed cryovial explosion - use them in liquid phase (Tomlinson and Morroll, 2008)



Professional Liability/ Human Error*

Association of Clinical Embryologists UK
(Tomlinson and Morroll, Human Fertility, 2008)

30% of industry staff received any formal training (senior staff local H&S)
 <5% from recognised gas suppliers

10% trainees - had anxiety over N2 use
45% senior staff - " " " "

Unaware of regulations

'Embedded lack of basic knowledge' - At risk

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Injury to personnel

UK Embryology/andrology staff :

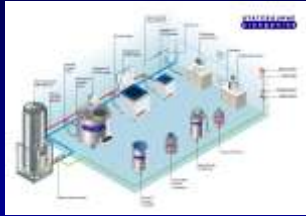
- Lack of engagement with the institution
- Poor awareness of any risk management process
- Facilities poorly sited (5th floor)
- Transport of nitrogen (elevators/stairs)
- Delivery vessels injuring portering staff
- Concerns over lack of space
- Ineffective extraction/O₂ monitoring
- Lack of PPE or use of PPE

*High risk - Despite heavy regulation and licensing of clinics

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Injury to personnel - Management cont'd

- Location - ground floor (avoid elevators BCGA)
- External wall - delivery
- Forced air extraction
- Oxygen monitoring
- Servicing
- Training



Courtesy of Statebourne Cryogenics UK

Major risk associated with Cryopreservation of Human cells and tissue

1. Injury to personnel

2. Loss of stored material

3. Damage to stored material

4. Misidentification of material

5. Risk to recipient/ART errors

5. Financial

6. Regulation

7. Quality Assurance

Loss or Damage to stored material

1. Freezing method

2. Storage

- Nitrogen Supply
- Equipment failure
- Audit/labelling

3. Breach of packaging (Contamination)



Loss or Damage to stored material

1. Cryopreservation

• Appropriate method

- Avoid contamination (grade A air)
- Optimised cooling rates

• Appropriate packaging

• Validation

- Scientifically justified
- Proven efficacy

40% IVF units had freezer failure at egg retrieval (<60% controls) in place

Tomlinson and Morroll, 2008

• Appropriate equipment Spare freezer/Contingency

Loss or Damage to stored material

2. Storage Risk

- Nitrogen Supply
- Equipment failure
- Identification and Audit
- Contamination

Loss or Damage to stored material

Liquid nitrogen supply

- Delivery failure
 - Natural disaster
 - Breakdown
 - Other
- Delivery vessel failure
- Staff failure
- Autofill system failed





Loss or Damage to stored material

Liquid nitrogen supply

Autofill systems

- Requires vigilance
- Vapour or liquid phase units
 - Solenoid blockage
 - Faulty controller
 - Faulty sensor
- Failure to fill
- Fill one preferentially (warm another)

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Loss or Damage to stored material

Liquid nitrogen supply Controls and Management

Deliveries

- Regular delivery to more than cover usage
- Excess storage capacity/spare supply vessel
- Bulk storage (autofill - vapour storage)



Manual fill

- Regular documented filling rota
- Regular inspection
- Document losses from each vessel (slow vacuum loss)

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Loss or Damage to stored material

Equipment Failure

Vacuum failure - rare???

UK reports - 2 dewars acute failure in 15 yrs

- Pressurised vessels
- Dewars
- Vapour units
- Dry shippers

- Controller failure (vapour units)
 - 3 major incidents/4-5 years
 - Ongoing Litigation
 - Dry shippers (couriers, keep upright)

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Loss or Damage to stored material

Equipment Failure Controls

- Divide precious specimens across vessels
- Have spare capacity
- Alarm and monitor vessels
 - Out of hours warning system
 - Formal staffing rota
- Avoid trauma
 - Flooring (smooth, no trip hazards)
 - Protect shippers - clear filling and transport procedure/instructions

Loss or Damage to stored material

Identification and Audit

- Poor labelling/Misidentification
 - Patient/recipient error
 - Apparent specimen loss (regulatory, litigation)
 - Warming between fingers

Loss or Damage to stored material

Identification

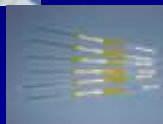
1. Label Missing

- Broken packaging
- Label detachment



2. Poor Labelling

- Transcription errors e.g 5 or S
- Illegible markings/handwriting
- Misaligned markings/bar code



Loss or Damage to stored material

Identification Risk Management

Controls

- Automated Labelling
- RFID (Radio frequency identification)
- Witness verification
- Robust labels - adheres to packaging in LN2

Doubts over identity

- Discard
- Record as incident

Loss or Damage to stored material

Storage review/audit

Mislabelling/Misidentification

"storage centres are expected to carry out reviews at least annually of the status of stored gametes and embryos"
HFEA code of practice, 6th Edition

ACE survey Tomlinson and Morroll (2008)
Andrology/Embryology Audit

- >50% - observed ejection of sealing plugs
- <60% - procedures for observation at -140 or below
- Few used PPE

'Risk to sample harm outweighs the benefits gained from audit'
Allow centres a flexible risk based approach depending on size/type of inventory

Loss or Damage to stored material

Breach of Packaging

Effect of LN2 on materials

Contamination

Loss of material

Hepatitis B incident 1995



Tissue banks and Blood service

- Storage system (vapour)
- Packaging (double skins)
- Screening**

Summary

- Risk assessment necessary or scaremongery?
- Identify potential hazard formally - even if low risk
- Hazards with low risk - no controls
- Hazards with high risk - implement controls
 - SOPs
 - training
 - Equipment/materials
 - facilities
- Institute support easier with formal risk assessment
