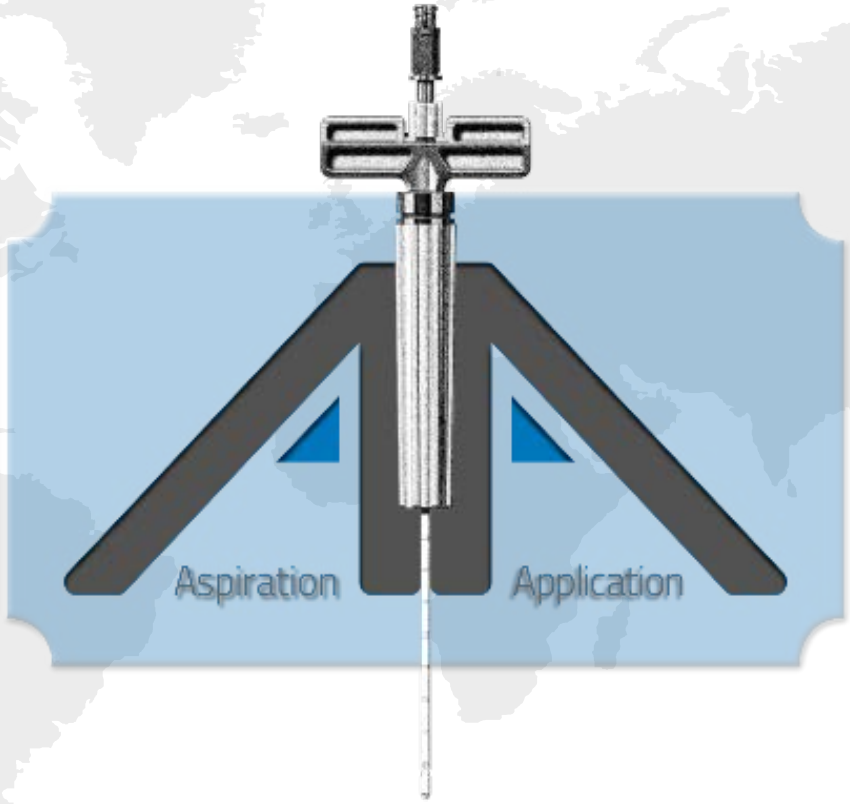
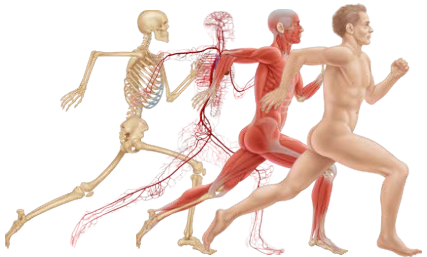
Marrow Cellution™

Autologous Bone Marrow Aspiration & Cancellous Bone Graft Harvesting

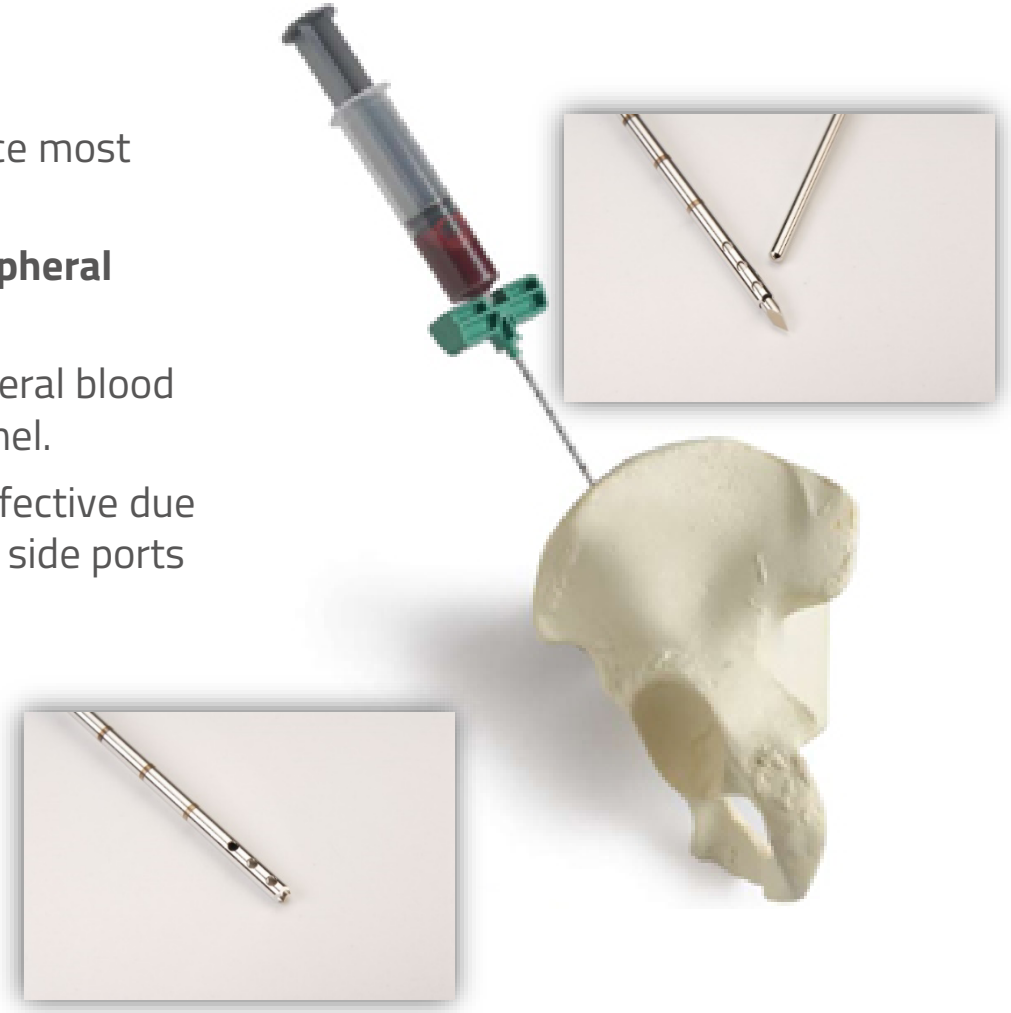




Traditional Trocar Design & Technique

The path of least resistance is the physical pathway that provides the least resistance to motion by a given object or entity, among a set of alternative paths.

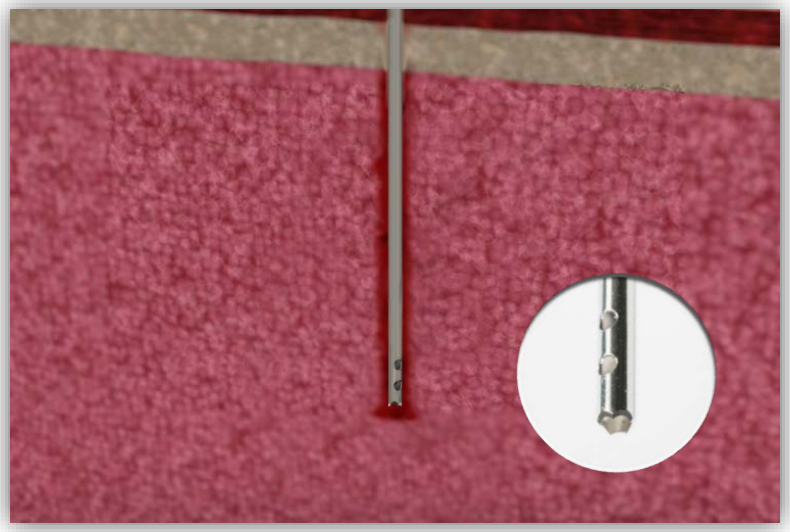
- Designed to perform a **single small volume pull (1-2mL)** from the distance most proximal from the entry of the needle.
- **Larger volumes** of bone marrow aspirate contain **higher amounts of peripheral blood** as the cannula is open ended.
- Aspirating after **retracting the needle exacerbates the problem** of peripheral blood contamination by exposing the open ended cannula to the resulting channel.
- **Side Port Fallacy**: Integration of side ports on traditional needles are ineffective due to the stronger forces associated with aspiration from distal end blocking side ports from within the lumen of the needle.



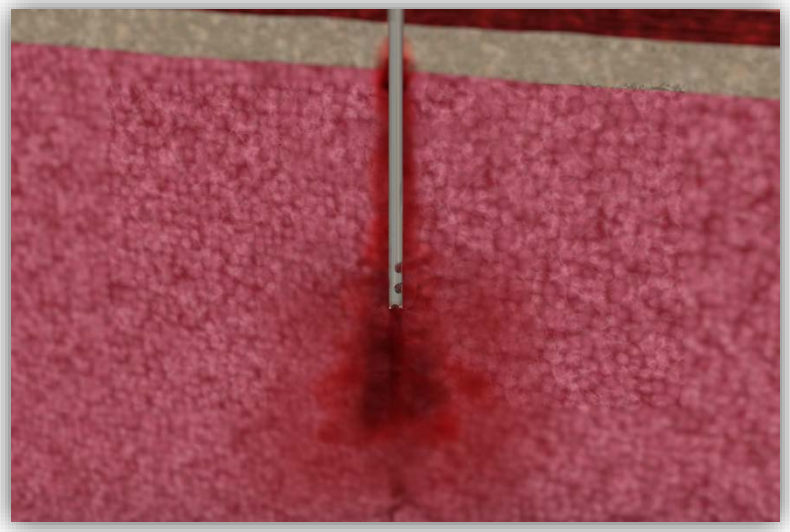
Traditional Bone Marrow Aspiration Techniques

Open End (Distal) Trocar with Side Port Fallacy

The regenerative qualities of bone marrow have been used for many decades and are considered the gold standard for stem cell harvesting.



Traditional open ended (distal) trocar designed aspiration needles operate optimally for small biopsy volumes of 1-2mL. After aspirating the first 1-2mL of bone marrow, peripheral blood will preferentially fill the vacated space, limiting the additional harvest of key stem and progenitor cells.



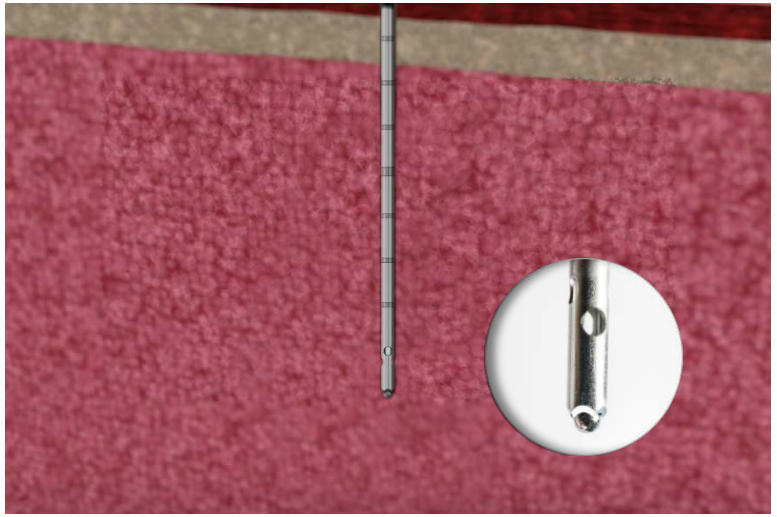
Further aspiration attempts diminish the number of total nucleated cells (TNC) in the aspirate drops dramatically due to the lower viscosity of blood following the path of least resistance through the distal end channel, minimizing efficiency of side channels.

Aspiration of larger quantities of bone marrow, typically required for most clinical indications, necessitate further manipulation and volume reduction processing steps such as, centrifugation systems or chemical gradient separation in a laboratory.

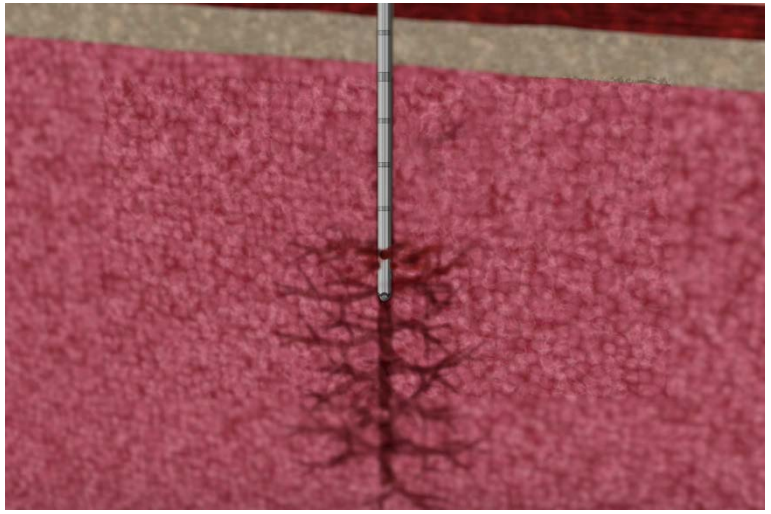
Marrow Cellution™ Solution

Marrow Cellution™ Overcomes Limitations & Maximizes Cell Yield

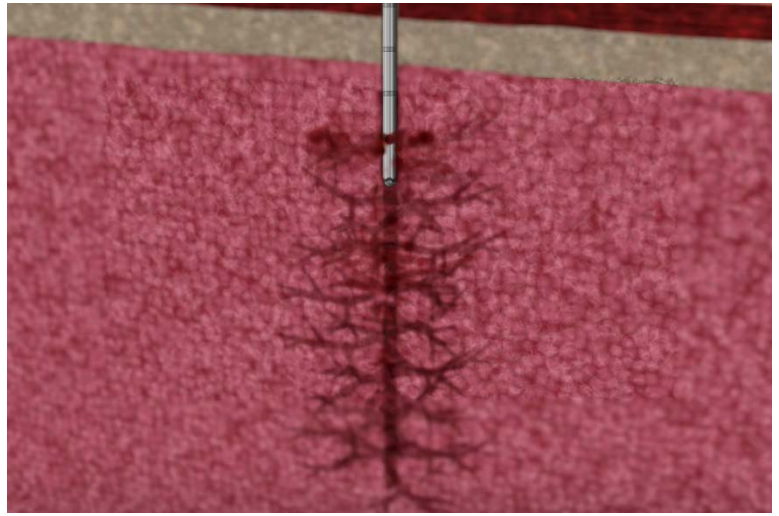
The unique patent pending techniques of implementing a closed end catheter through a introducer sheath overcomes distal end peripheral blood contamination.



The short sharp trocar introducer allows for easy access through soft tissue and cortical bone. A blunt trocar is then introduced to make access for closed end side port aspiration cannula. The design minimizes trauma to cancellous bone and marrow, thereby mitigating pooling of peripheral blood.



The patent pending design of the closed end catheter forces aspiration of marrow from lateral marrow space. The manual rotation of the handles allows the cannula to be raised to a desired position in a new level of undisturbed marrow for subsequent aspiration aliquots.

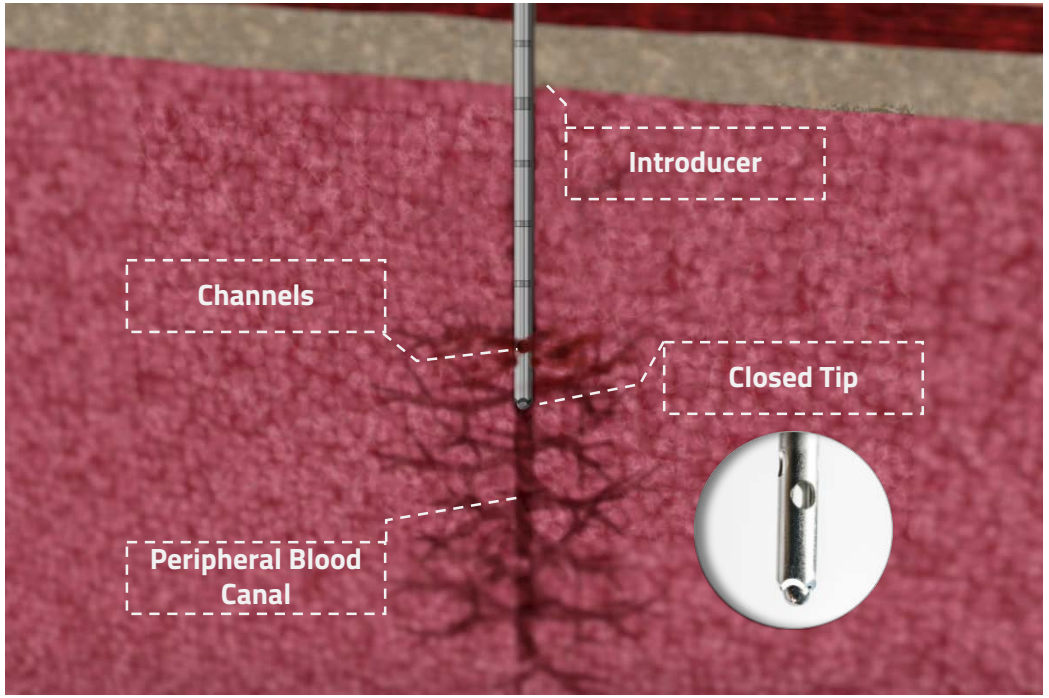


The Marrow Cellution™ is able to collect up to 10mL of high quality marrow equivalent or superior to other systems that require additional manipulation steps such as centrifugation or chemical separation in a laboratory.

Marrow Cellution™

Overcome Limitations & Maximize Cell Yield

- Marrow Cellution is a novel bone marrow access and retrieval device that incorporates unique features designed to minimize the limitations of traditional trocar needles.
- Aspirate flow is collected exclusively laterally as the tip of the aspiration cannula is closed allowing marrow collection perpendicular to and around the channel created by the tip of the device.
- Marrow Cellution achieves multiple small volumes of high quality bone marrow aspirate collected from various sites distributed within the marrow cavity.
- A single puncture with Marrow Cellution is functionally equivalent to repeated puncture sites with a traditional trocar needle collecting small aspirate volumes, but with substantial savings of time, effort, reduced patient trauma, morbidity and risk of infection.

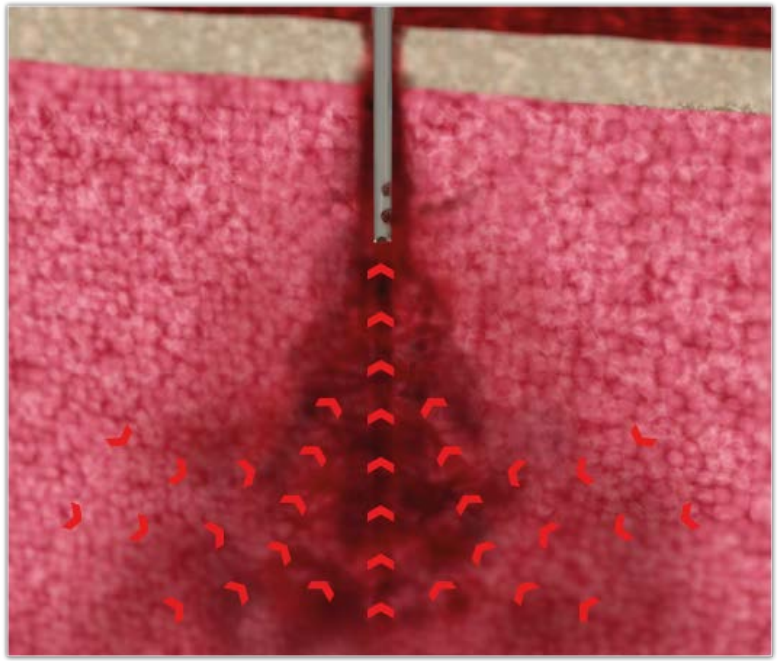


Patent Pending Design
Four channel, closed tipped, aspirating cannula prevents exposure of the needle tip to the channel filled with peripheral blood created by the needle as it is being retracted from the bone space.

Overcoming Limitations

Overcome Limitations & Maximize Cell Yield

The innovative Marrow Cellution™ System allows for specific aspiration to eliminate peripheral blood contamination and thereby significantly improving cellular yield performance.



Aspiration of larger quantities of bone marrow, typically required for most clinical indications, necessitate further manipulation and volume processing steps such as, centrifugation systems or chemical gradient separation in a laboratory.

PERFORMANCE

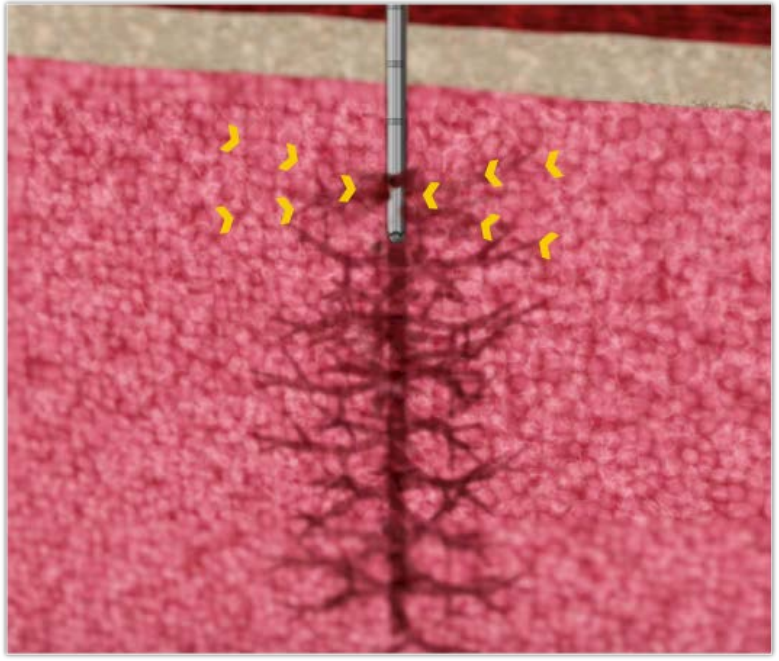
- ✓ High Quality – Low Volume
- ✓ Higher CFU counts per mL
- ✓ Additional steps not required
- ✓ No Anticoagulant Contamination

INNOVATIVE

- ✪ Reduces peripheral blood aspiration
- ✪ Closed-end aspiration design
- ✪ Cannula via sheath technology
- ✪ Novel patent pending design

SPECIFIC

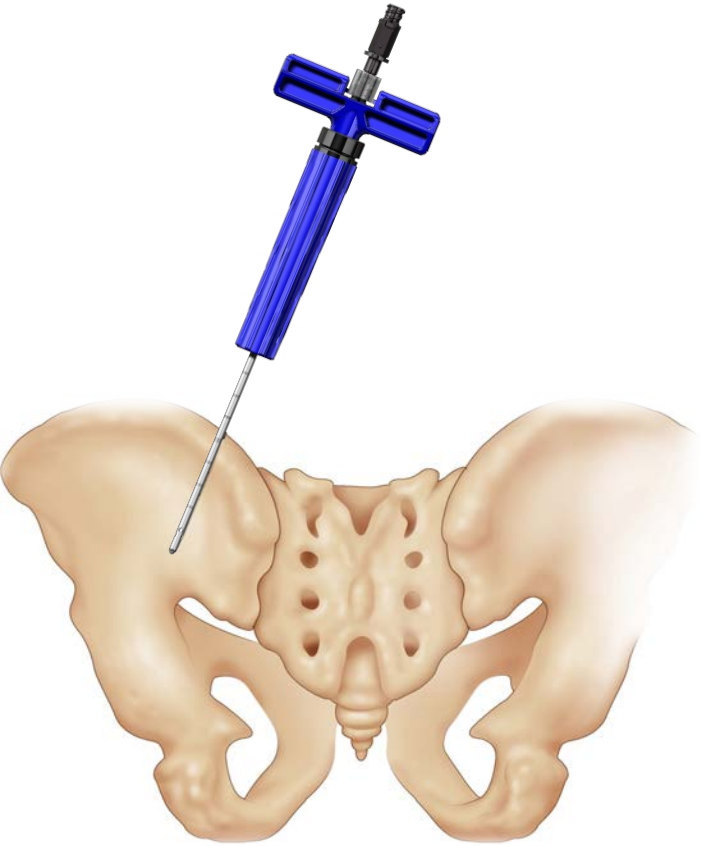
- ⌖ Minimally invasive
- ⌖ Minimizes OR Time
- ⌖ Maximizes Sterility Conditions
- ⌖ Low volume
- ⌖ High yield
- ⌖ Reduces Biologic Utilization Costs



The Marrow Cellution™ System is able to collect up to 10mL from each puncture site of high quality marrow equivalent or superior to other techniques that require additional manipulation steps such as centrifugation or chemical separation in a laboratory.

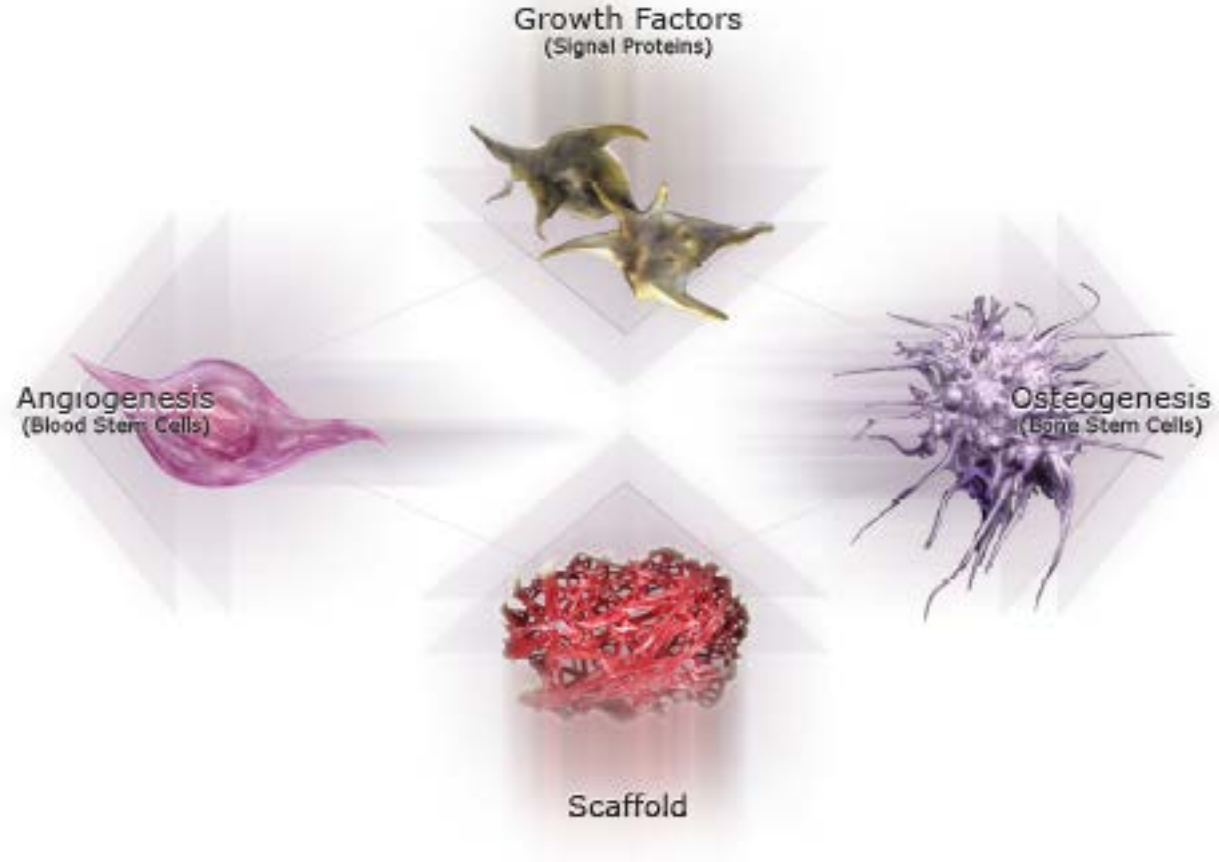
Marrow Cellution

Essential Healing Factors



Source: A. Caplan

Impaired Angiogenesis Results in Impaired Healing.



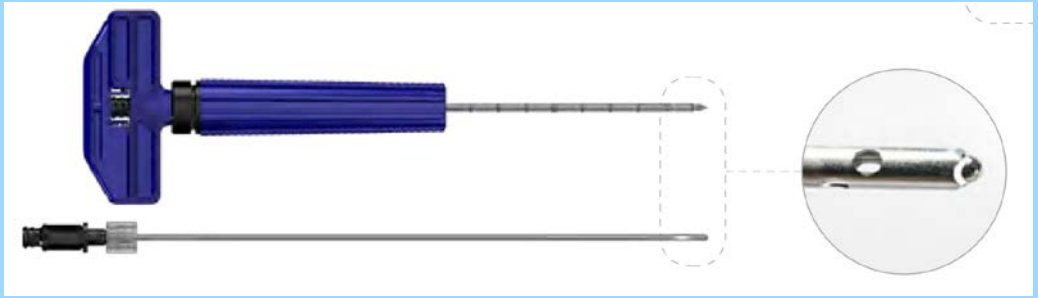
Creating a rich microenvironment with vascular sufficiency is a critical, well established first step in bone formation.

Autologous Bone Marrow Aspiration & Bone Graft Harvesting

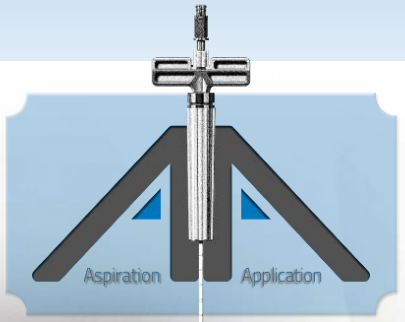
MARROW CELLUTION

OVERCOME LIMITATIONS & MAXIMIZE CELL YIELDS

Unsurpassed Cell Collection



Cancellous Graft Collection



Fusion

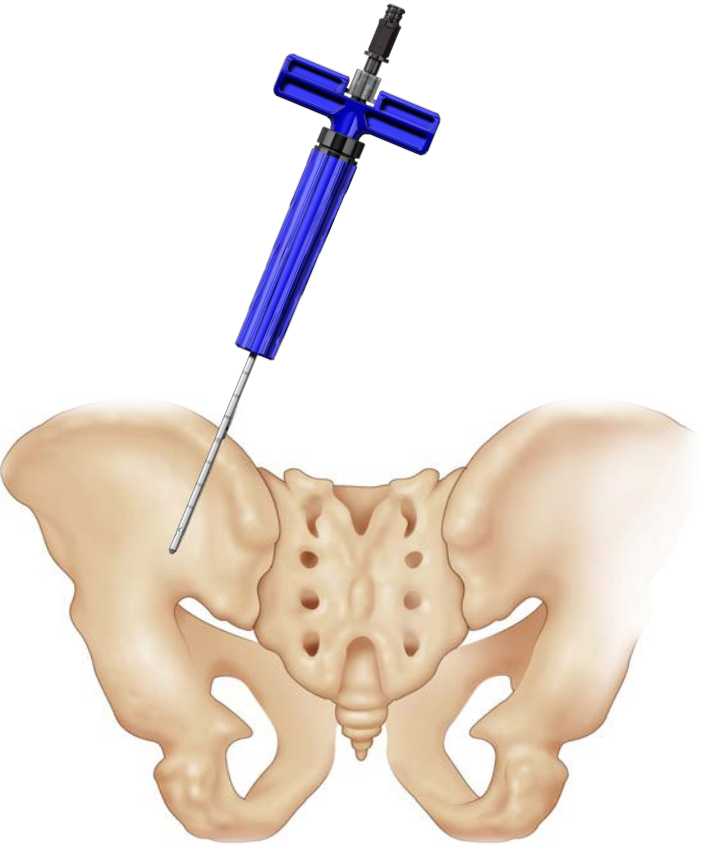
VS.

Failure

- ✓ Maximizes Cell Yield
- ✓ Minimally Invasive
- ✓ Centrifugation Not Required
- ✓ Never Leaves the Sterile Field
- ✓ Reduces Blood Contamination
- ✓ Regulatory Compliant
- ✓ Reduces Donor Site Morbidity
- ✓ 100% Natural

Marrow Cellution

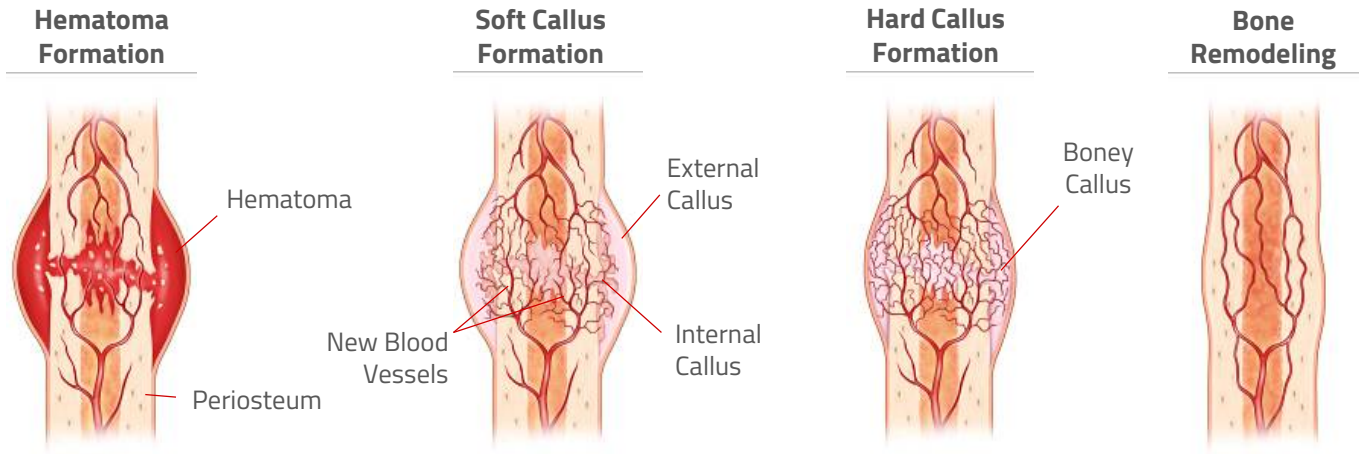
Bone Healing Biology



Source: A. Caplan

"The mechanism of action in bone healing points to the hierarchical role of creating a vascular network before bone can be formed"

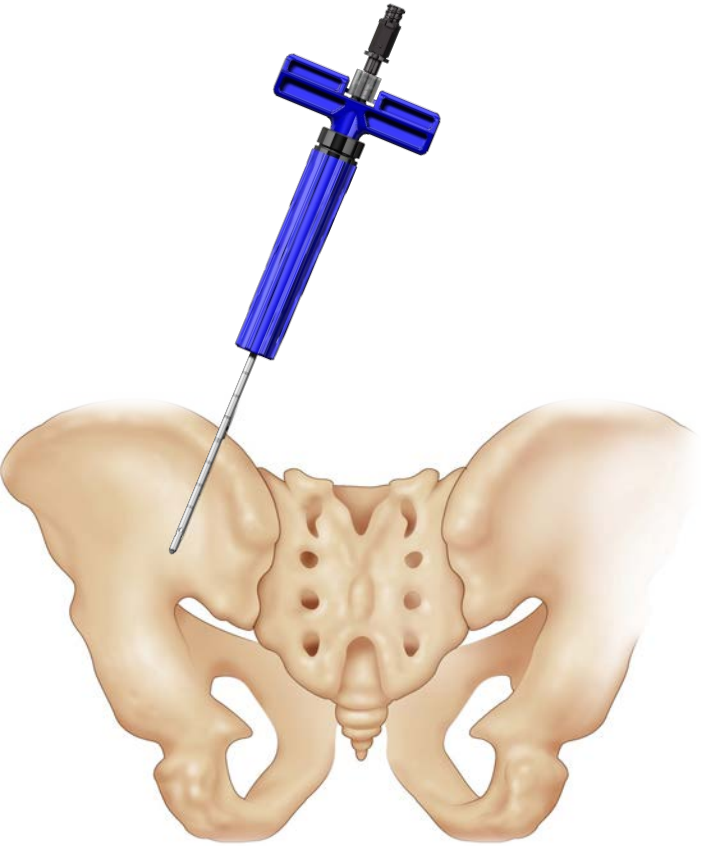
Creating a microenvironment with vascular sufficiency is a critical first step in bone formation since impaired angiogenesis results in impaired bone formation.

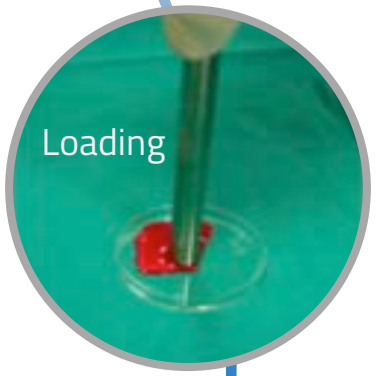


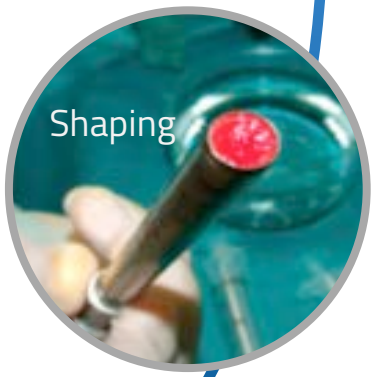
BONE GRAFTING PROCEDURE	=	AUTOLOGOUS BONE GRAFT HARVEST & TRANSPLANTATION
Marrow Cellution	=	Minimally Invasive Bone Graft Composition (Liquid & Cancellous)

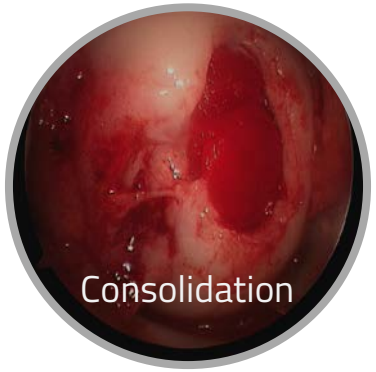
Marrow Cellution

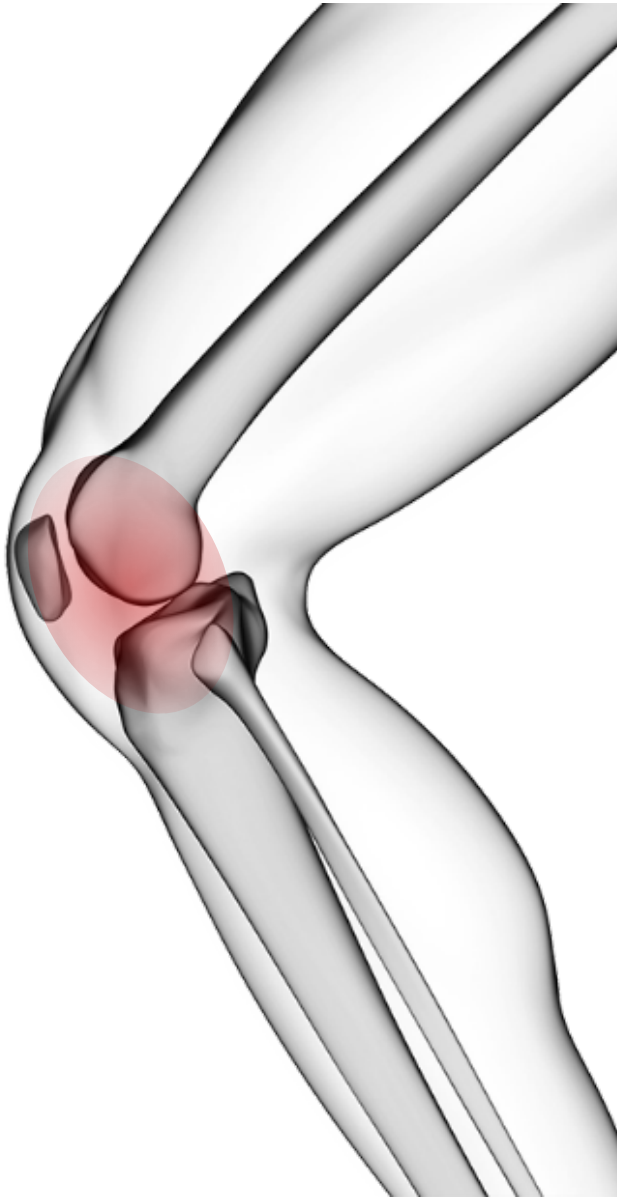
Subchondral Bone Healing











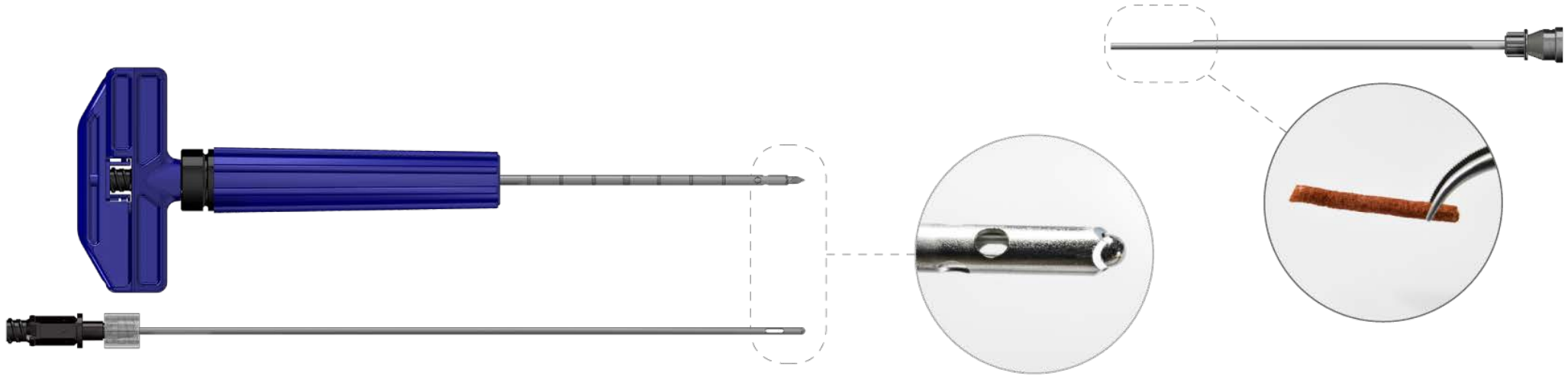
Source: Buda R. et al. J Bone Joint Surg Am. 2010;92:2-11.

Marrow Cellution: Striking Advantages

Autologous Cell Collection & Cancellous Bone Grafting

The functional design of the Marrow Cellution™ System includes two unique features: a **Closed Needle Tip** to prevent aspiration of excess blood from the entry channel and a **Handle With Threaded Guide** for controlled movement of the aspiration cannula within the marrow space.

The MC-RAN-8C Marrow Cellution™ System provides the additional benefit to **Percutaneously Harvest Bone Graft** in the same minimally invasive procedure. Thereby, reducing donor site morbidity.



Marrow Cellution™

Marrow Cellution™ Bone Marrow Aspiration System (MC-RAN-11C).

Allows for measured and controlled aspiration over a large geography within the marrow space, while **restricting peripheral blood infiltration**.

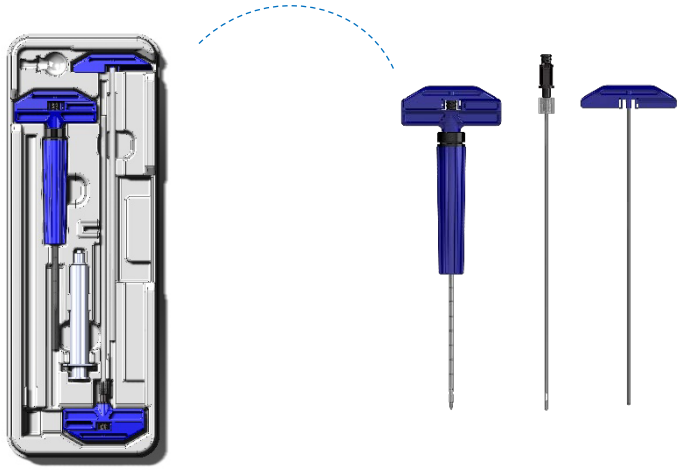
Marrow Cellution™ Bone Marrow Aspiration- & Autologous Bone Harvesting System (MC-RAN-8C).

Allows for the combination of high quality **bone marrow aspirate** and percutaneously harvested **cancellous bone autograft**.

"This is potentially a giant step in bone marrow processing. This needle will usher in a new age in bone marrow aspiration."

Dr. Joseph Purita, M.D.
Orthopedic Surgeon, Boca Raton/FL

Marrow Cellution™ Product Details

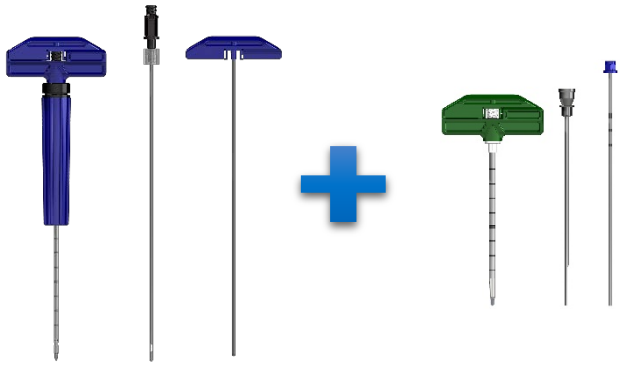


MC-RAN-11C
Item #: 74219-06M
Effective Length: 3.5" (9cm)

Components:
- 11 Gauge Introducer Cannula & Sharp Stylet
- 11 Gauge Introducer Blunt Stylet
- 14 Gauge Aspiration Cannula
- 10mL Syringe

MC-RAN-11C STS (OBESE PTS.)
Item #: 74219-07M
Effective Length: 4.5" (11.4cm)

Components:
- 11 Gauge Introducer Cannula & Sharp Stylet
- 11 Gauge Introducer Blunt Stylet
- 14 Gauge Aspiration Cannula
- 10mL Syringe



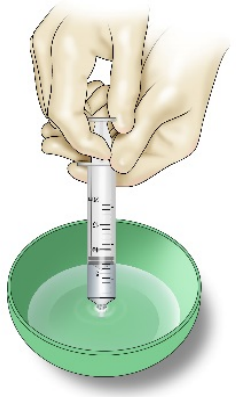
MC-RAN-8C
Item #: 74266-01M
Effective Length: 3.5" (9cm)

Components:
all MC-RAN-11C components and
- 8G x 4" Swaged Tip Introducer Needle
- Measurement Probe
- Cancellous Bone Dowel Extraction Tool

MC-RAN-8C STS (OBESE PTS.)
Item #: 74266-04M
Effective Length: 4.5" (11.4cm)

Components:
all MC-RAN-11C components and
- 8G x 6" Swaged Tip Introducer Needle
- Measurement Probe
- Cancellous Bone Dowel Extraction Tool

Component Flushing (Rinsing) Instructions



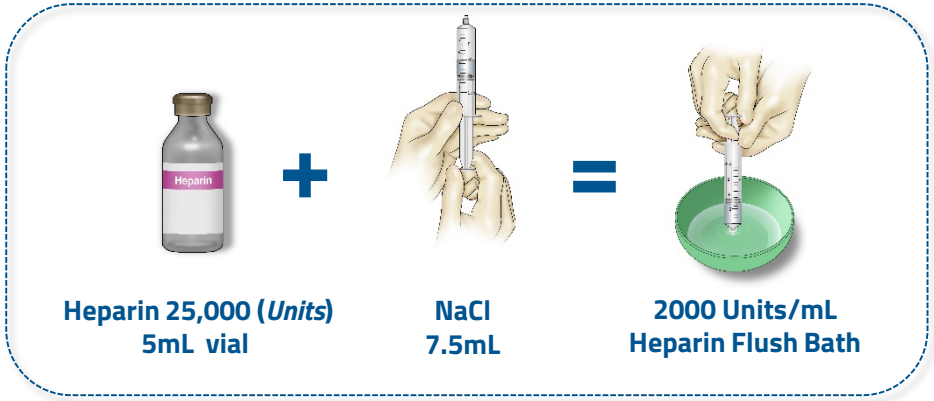
2,000 Units/mL
Heparin Flush Bath

- Withdraw approximately 5-7mL of Heparin Solution (2,000 units/mL) into 10mL syringe
- Remove Stylets from Introducer Needle and Aspiration Cannula with distal end of needle inside sterile bowl
- Connect Heparin-filled syringe to the shorter Introducer needle and inject Heparin until needle is fully rinsed.
- Aspirate Heparin back into syringe and disconnect from needle.
- Repeat for the longer aspiration needle.
- Rinse each stylet, short introducer sharp and blunt, longer aspiration stylet.
- With needle guards in place, rinse the outside of each needle by injecting Heparin into the open end of the guard.

Heparin Flush Protocol

Preparation of a Heparin Flush Bath

- Obtain a 5mL vial of 5,000 units Heparin per mL (25,000 units in total).
- Using syringe, empty the 5mL into a sterile bowl.
- Add 7,5mL of sterile saline to bowl.
- Bowl contains 12.5mL of 2,000 units Heparin per mL
- Summary: 25,000 (Units) / 12.5 (mL) = 2,000 Units/mL



Alternate Preparation

- Obtain 10mL of 1,000 unit per mL Heparin (10,000 units in total).
- No dilution required.

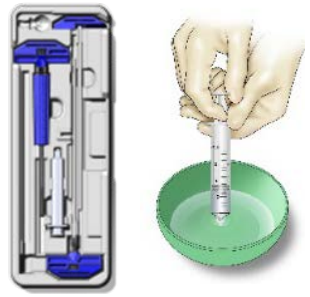
It is important that the strength per mL of the heparin rinse is at least 1,000 but **preferably 2,000** and that you have adequate volume to rinse all of the needles and syringes.

Bone Marrow Aspiration Process Steps

Marrow Cellution™

1

Heparin Flush:
Rinse all components with heparin (2,000 Units/ml)



2

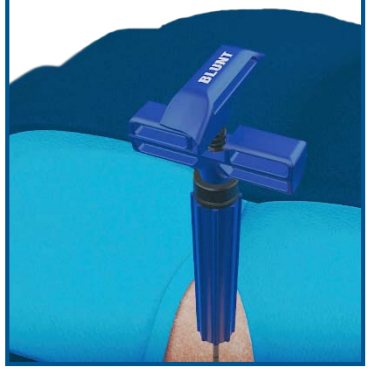
Insert Access Needle just past cortex into medullary space.
Ensure longitudinal orientation.

3

Remove Sharp Stylet, attach Syringe, draw 1ml marrow to test proper localization of Access Needle tip

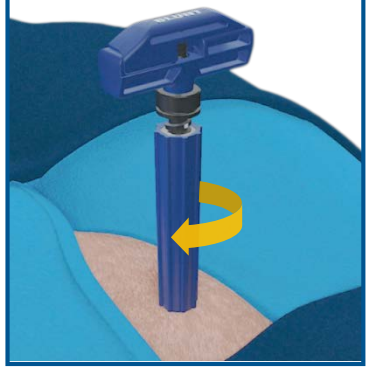
4

Remove Syringe, insert Blunt Stylet. Continue to advance Access Needle to desired depth



5

Rotate Guide Grip to skin level and remove Blunt Stylet



6

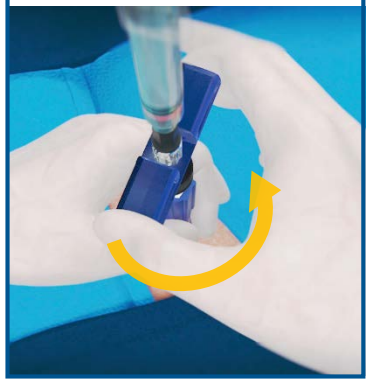
Remove Blunt Stylet, insert and attach Aspiration Cannula.

7

Attach Syringe, draw 1ml marrow

8

Rotate handle 180°-360° counter clockwise to raise Cannula tip



9

Draw 1ml marrow

10

Repeat steps 8 & 9 until desired volume is attained

ASPIRE MEDICAL INNOVATION

Abbreviated Instructions Overview.
Information for Healthcare Professionals only.
Refer to package insert for complete Instructions for Use.

For further information please contact your local Marrow Cellution representative or consult www.aspire-medical.eu

Manufacturer:
Ranfac Corp..
30 Doherty Avenue
Avon/MA 02322, USA
www.ranfac.com

EU-Representative:
Aspire Medical Innovation GmbH
Einsteinstraße 167
D-81677 Munich
www.aspire-medical.eu

CE 0086

Hospital for Special Surgery (HSS): Dr. Joseph Lane, Comparison

AAOS 2013 Poster: Journal of Orthopedic Trauma (*submission*)

Aspiration to Application without Centrifugation

Count	Harvest	Biomet	Harvest	Arteriocyte	Marrow Cellution
	Series 1		**Series 2**		**Snap Aspiration**
	Aspirate: 60mls, Concentrate: 7mls		*Aspirate: 60mls, Concentrate: 7mls*		*Aspirate: 5mls*
Nucleated Cell Count (million/ml)	101,48	90,81	90,80	38,17	**80,0**
Absolute CFU-F Count	7.100	806	8.888	3.600	**38.800**
CFU-F/ml	1.014	134	1.270	514	**7.760**

1ml of Marrow Cellution (CFU-F/ml=7,760) contains the same CFU-F Volume compared with the final output after „point of care“ processing of aspirated marrow (60mls) reduced to 7mls of concentrate.

What is the importance of CFU-f counts compared to nucleated cell counts?

CFU-f

- There is no constant ratio between average marrow cellularity as measured by number of total nucleated cells per mL and the number of CFU-f. Hernigou et al in several authoritative studies linked clinical outcomes in non-union and osteonecrosis to the number of CFU-f cells in the graft.
- Controlling for volume, Hernigou et. al. noted that 70% of the variation in CFU-f from patient to patient was due to variations in the quality of the marrow aspirate or idiosyncratic to the patient with the remaining variation being due to the of number of nucleated cells per mL in the aspirate.
- Statistically, the only variable Hernigou reported to be significant was CFU-f and not nucleated cells per mL. Interestingly, CFU-f is found frequently in marrow and very rarely in peripheral blood.
- "Therefore, it seems reasonable to suggest that a graft needs to contain greater than 1000 progenitors/cm^3" (P. Hernigou).

References::
Hernigou P, et al. Treatment of Osteonecrosis with autologous bone marrow grafting. Clinical Orthopaedics and Related Research. Number 405, pp 14-23
Hernigou P, et al. Percutaneous Autologous Bone-Marrow Grafting for Non-unions – Influence of the Number and Concentration of Progenitor Cells. The Journal of Bone and Joint. Volume 87-A, No 7, July 2005

Comparative Results

System	Hernigou Cobe	Harvest SmartPReP™	Marrow Cellution™
Aspiration Volume	306mL (Mean)	120mL (Mean)	10mL or **20mL**
CFU-f in Aspirate	612/mL (Mean)	485/mL (Mean)	2275/mL
Concentrate Volume	20mL (Mean)	15mL (Mean)	10mL or 20mL (Unchanged)
Total CFU-f Delivered in Concentrate	2,579/mL (Mean) Range: 1,458 - 3,700 /ml	3,200/mL (Mean) Range: 2,500 - 4,100 /ml	2,275/mL (Unchanged)
Yield of CFU-f in Concentrate	27.5%	82 %	100%
CFU-f Delivered to Non-Union Site	**51,589 (Mean)** Range: 34,149 - 74,000	**48,000 (Mean)** Range: 37,500 - 61,500	22,750 in 10mL **45,500 in 20mL**

Source: Hernigou / Harvest Comparison with Marrow Cellution Data

Competitive Performance

CFU-f Cell Count Comparison

References:

(1) n=5; Scarpone MA, et al. Marrow Cellution Bone Marrow Aspiration System and Related Concentrations of Stem and Progenitor Cells. White Paper 2015.

(2) n=27; Harrell DB, Purita JR. Novel Technology to Increase Concentrations of Stem and Progenitor Cells from Marrow Aspiration. White Paper 2016.

(3) Hegde V, et al. A prospective comparison of three approved systems for autologous bone marrow concentration demonstrated non-equivalency in progenitor cell number and concentration. J Orthop Trauma. 2014 Oct;28(10):591-8.

(4) McLain R, et al. Aspiration of Osteoprogenitor Cells for Augmenting Spinal Fusion: Comparison of Progenitor Cell Concentrations From the Vertebral Body and Iliac Crest. J Bone Joint Surg Am. 2005 Dec; 87(12): 2655–2661.

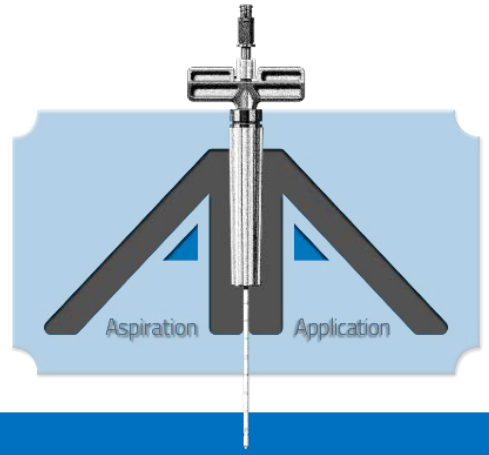
CFU Counts

Additional Field Samples

Lab	Orientation	Volume (mL)	TNC ($x10^6$)	CFU-f / mL	Total CFU-f in Graft
CBR	Anterior	8	29.72	1,039	8,316
CBR	Anterior	8	36.44	4,513	36,107
UT	Posterior	8	42.00	1,146	9,168
CBR	Posterior	10	21.60	1,199	11,990
CBR	Posterior	10	24.00	1,999	19,990
Franciscan	Posterior	10	45.00	4,222	42,222
Franciscan	Posterior	10	31.00	3,400	34,000
Franciscan	Posterior	10	22.00	3,000	30,000
CBR	Posterior	10	18.00	630	6,300
CBR	Posterior	10	25.22	814	8,144
CBR	Posterior	10	32.44	804	8,044
			Average	2,070	19,480

Source: Validation Samples via Independent Laboratories

Quick Fact Sheet

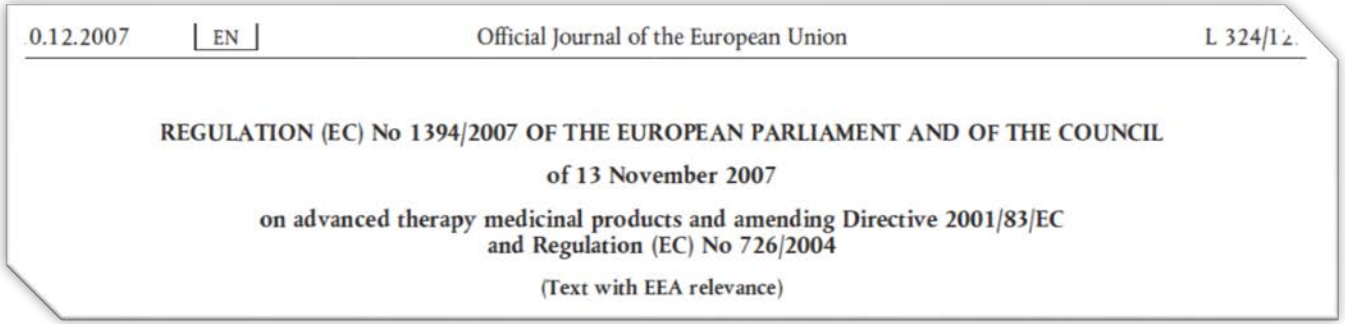


	Marrow Cellution™	Centrifugation Systems
Time	5 minutes	45 minutes
Invasiveness	10mL	60mL – 240mL
Efficiency	100% Utilizable	85% Discarded 15% Utilizable
Contamination Risk	100% Sterile Field	Offsite Processing
Peripheral Blood Contamination	Minimal	High
Personnel Time and Training	None	Extensive
Technique Sensitivity	No	Extensive
Regulatory Compliance	Compliant	Advanced Therapy Drug

Regulatory Compliance Becoming Increasingly More Restrictive

Advanced Therapy Medicinal Product (ATMP)

Regulatory Review & ATMP Assessment



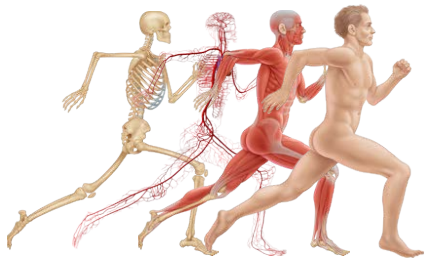
0.12.2007 EN Official Journal of the European Union L 324/12

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)



Aspire Medical Innovation
Einsteinstr. 167
D-81677 München

Regulatory Compliance EU Reg: 1394/2007

Definition of ATMP

Advanced Therapy Medicinal Products

- Gene Therapy Medicinal Products (GTMP)
- Somatic Cell Therapy Medicinal Products (SCTMP)
- Tissue Engineering Products (TEP)
- Combined ATMP's and Medical Devices

Gene Therapy Medicinal Products and Somatic Cell Therapy Products defined in Annex 1 to Directive 2001/83/EC

- Tissue Engineering Products: "Tissue engineering is the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules" Defined in Reg: EU No. 1394/2007

EU Regulation 1394 / 2007

Do I have an ATMP according to EU 1394/2007 Regulation?

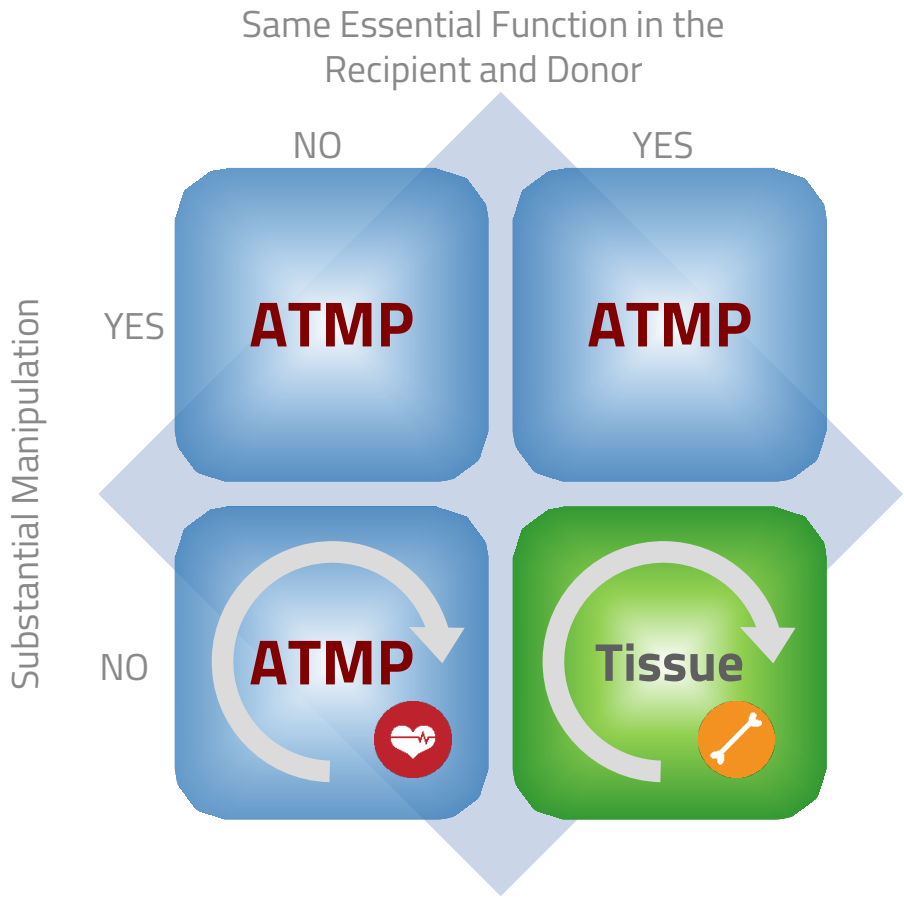
ATMP Definition:

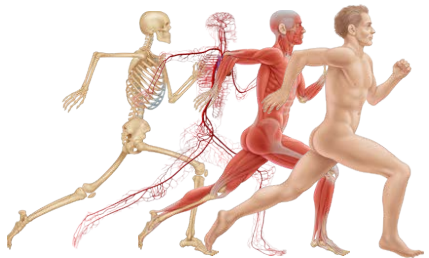
Contains or consists…

…of cells or tissues that have been subject to ***substantial*** *manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered,*

or…

…of cells or tissues that are not intended to be used for the ***same essential function****(s) in the* ***recipient*** *and the* ***donor (Homologous Use)****;*





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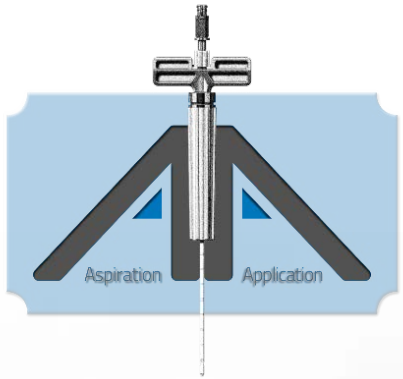
Marrow Cellution System



- ✓ Maximizes Cell Yield
- ✓ Regulatory Compliant
- ✓ Centrifugation Not Required
- ✓ Never Leaves the Sterile Field
- ✓ Reduces Blood Contamination
- ✓ Reduces Donor Site Morbidity

Marrow Cellution™ provides substantial savings in time, effort and expense.
It reduces patient trauma, morbidity and risk of infection.